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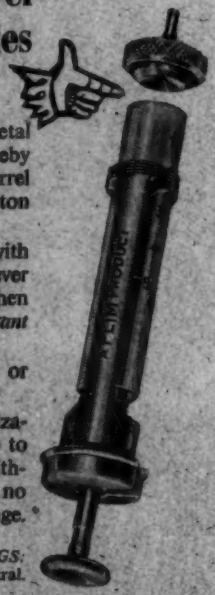

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BRITISH MEDICAL JOURNAL

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THE PHENOMENA OF EPILEPSY*

BY

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The question, "Is this epilepsy?" seems to be asked more often and in more various circumstances than it used to be. It may simply relate to attacks of unconsciousness, or to focal disturbance of movement or sensation, but, even so, the answer is unusually important because of its social and economic implications to the patient and his family, quite apart from the problem of treatment and management. Other groups of people are interested too. Employers want to know, sometimes more to safeguard themselves than to protect the patient; public servants have to administer insurance and superannuation regulations; armed Forces have to protect their efficiency from the sudden disruption of a fit or the administrative consequence of its recognition. Teachers want to prevent their pupils from seeing an epileptic attack in another to the ruination of his own schooling; or lovers about to mate calculate the risks of procreation in this respect.

With the assumption of social responsibility by others, and with a more enlightened approach to the study of antisocial and aggressive behaviour, many more people became interested in the answer. Those philanthropists who were concerned about crime and the criminal recognized that some aberrant behaviour or abnormal thoughts might be epileptic, that a cause might be found, and chemical treatment prove successful where psychiatric and social had failed. The child psychologist studying a child with temper tantrums asked whether this might be epileptic. The prison medical officer faced with an intractable Borstal problem, or the psychiatric physician dealing with a long story of intermittent unusual behaviour, has been faced with the same problem. Then lawyers, encouraged by the physicians for the defence in cases of comparatively gainless crime, advance the argument, "This may be epilepsy," so that finally the judge or his jury have to answer the question.

The Diagnosis of Epilepsy

With all this, the ordinary doctor had been seeing many ordinary patients with attacks of loss of memory or consciousness, of muscle-twitching, of feelings of faintness or of unreality, or of transient disturbances of vision, for every unusual one who presented a social problem. Usually there are no physical signs to help him in this diagnosis, for the patient is well when he tells his story, so that he must base his opinion on minute retrospective facts found by careful questioning of subject and observers. The true interpretation lies in deduction, with the same scrupulous regard for facts as is found in police detection. It is rarely that this method fails, and, allowing the place of experience of the usual and unusual in arriving at a correct diagnosis, the neurologist may succeed simply by taking a more careful history and by sticking to the evidence he has found. In the unusual case, diagnosis may at the time be impossible for want of evidence, or in doubt because of its nature. When this is so, opinions may be given too freely, the term "epilepsy" applied too carelessly; and, when such assumed accuracy seems dishonest, diagnostic uncertainty is expressed as "epileptoid states" or "epileptic equivalents"—phrases which reflect as great confusion of thought in the physician as there is confusion of feeling and behaviour in the patient.

How, then, is the diagnosis of epilepsy to be made? When the distinction is between a faint and a fit there may be no great difficulty, but when the diagnosis rests upon a story of complex disturbances of behaviour, or prolonged disorder of thought or feeling, it may be most bewildering. Clinical observation, aided by electrophysiology and experimental neurosurgery, has very widely expanded the recognized field of disorders caused by epileptic disturbances and has made many definitions worthless. We know that epilepsy can occur without loss of consciousness, without amnesia, without involuntary movement, and without any of the simple features which would enable us to make a certain diagnosis of epilepsy. None of the definitions will do, for they are all too narrow.

The Nature of Epilepsy

Whenever an epileptic disturbance is recognized by the patient or by others there is an abnormal discharge of electrical energy in the brain. It is more accurate to consider the disturbances which are seen in the electroencephalogram as the accompaniment of the disturbance experienced by or seen in the patient rather than as its cause. They are both related to the same cause. Lennox found so much difficulty in defining epilepsy that he called it a cerebral dysrhythmia, having in mind the disordered electrical rhythms invariably present in the attack. In fact, epileptic states are accompanied by a cerebral electrical dysrhythmia, and the electrical disturbances may be closely related to the nature of the clinical attack, but they are not the cause of the attack.

*Address to the Guildford Division of the British Medical Association given on December 11, 1952.

That is not now important; these discharges may occur anywhere in the brain—in the cortex or basal grey matter, in any of its lobes and gyri—and they may have one or a number of patterns of electrical rhythms.

Now all we do, think, or feel depends on our cerebral hemispheres. Simple movements such as a muscle twitch, or more complex ones such as a golf swing or a musical achievement, are mediated through the cells of the motor side of the cerebral integrative mechanism. On the sensory side, where movements are made possible and initiated, such crude sensations as pain or tingling; such complex ones as the awareness of the size, shape, position, and movement of a limb; and such intimate feelings as affection, elation, jealousy, or esteem—all have their physiological origins in cerebral cells. Strangely enough, although the close dependence of the intellectual level on the integrative efficiency of the cerebral hemispheres has been readily accepted, a similar dependence of parallel attributes of personality and behaviour is usually overlooked. This is probably because of the importance put on environmental influences by the dynamic psychiatrists.

It must surely be clear then, if the cortex is so intimately concerned with the whole activity of the organism, that these electrical discharges associated with epilepsy may accompany a disturbance of any movement, feeling, or thought that it is capable of, for they may arise in and spread over any part of the cortex. This cerebral disturbance may be a negative one—the negation of feeling which is unconsciousness—or a positive one—tingling, distorted feeling in a limb, or even an attack of fear or jealousy. Just as the movements of an epileptic attack are a travesty of normal movement because of the crude and unphysiological nature of the epileptic stimulus to the cortex, so the epileptic disturbances of sensation, of thought, or of feeling are caricatures of the normal.

The subject of an uncinate attack experiences an unpleasant indescribable smell that he has difficulty in recalling: unpleasant, because it is a crude complex of smellful sensations; indescribable, because it has not been evoked by a recognized stimulus—it is unnatural; difficult to recall, because it has been caused by an epileptic discharge passing over the olfactory cortex without an extraneous stimulus, and has not followed the integrative pathways within the cerebrum which lead to the storing of impressions, with consequent memory. "It was like nothing on earth, very real at the time, but I can't remember it now," they say. That is in the very nature of the epileptic disturbance. It reflects the ubiquity of the epileptic experience, with the crudeness of its electrical insult to the cortex and its disregard for normal cerebral physiology. We must not forget that, although the epileptic discharge may teach us about the response of the cortex to an abnormal discharge, at most it presents us with a caricature of normal cerebral functions.

What Epilepsy is Not

If what I have said is true, the epileptic attack accompanied by a sudden electrical storm in the cortex cannot have a direct relationship to preceding or succeeding normal events, whether these are in movement, feeling, or thought. The form of the attack is not determined by preceding events; the patient's behaviour after the attack does not flow naturally from it. The attack is an interruption in the flow of activity of the organism. That is why no epileptic attack is "motivated" and why no motivated act is ever epileptic. If intelligent purpose is inherent in an act, the underlying physiological process must have been that of sensory perception, leading to awareness, central integration of the experience, and then purposive movement. The epileptic discharge does not employ channels of neuronal activity in the brain in such a highly co-ordinated way as this, and it would be surprising if it did so.

Similarly, although epileptic movements or feelings may be fairly complex when the epileptic discharge is disturbing an area of higher motor or sensory integration in the cortex, the nature of the disordered function is related to the abnormal epileptic discharge itself as well as to the normal functions of that area of cortex, so that it is usually primitive and fragmentary. For instance, a discharge in a motor association area may cause such a fragment of behaviour as deviation of the eyes to the left, so that purpose is assumed by the observer in saying, "He looked to the left," or flexion of the index finger, which would suggest that the patient was beckoning. In fact, these incidents were devoid of purpose; they seemed purposeful because they arose in a part of the cortex which normally integrates movement into smooth and purposeful activity. When highly complex thought processes, emotions, or actions are experienced, and particularly when these follow each other in an expected, purposive, or reasonable and natural manner, they probably *are* purposive and in the circumstances reasonable, and not the accompaniment of such a primitive electrical discharge as that which underlies the epileptic state. Epileptic behaviour is always primitive, considered against the natural function of the part of the brain involved.

The epileptic experience is brief, fragmentary, and usually stereotyped. It comes out of a clear sky and fades into it, transient, purposeless, and unfinished. The post-ictal disturbance of consciousness may, however, last for many minutes, and sometimes in status epilepticus the patient may fall from one attack into the next with such brief intervals that it requires care and skill to recognize the individual attacks, but this can usually be done. Any one epileptic attack lasts for about the same time as the electrical discharge in the electroencephalogram, and, although all brief attacks are not epileptic, no continuous prolonged disturbances of behaviour, thought, or feeling are entirely epileptic in origin. I say entirely, because a patient may hit his head in an attack and so be confused for some time after, have another attack, or develop a hysterical disorder during the post-ictal period of lowered consciousness. The epileptic disturbance is in itself brief.

Lastly, because of its nature the epileptic state is episodic, and indeed one of the unsolved problems of the epileptic discharge is why it ceases, why it appears to be self-limiting The short stereotyped episodes are usually recognized because they stand out in clear contrast to the intervening normal behaviour.

It should now be clear that no positive definition can be applied to epilepsy, because the epileptic disorder may interrupt or mimic any aspect of normal movement, feeling, or thought. The content of an epileptic attack cannot be continuously related to preceding or subsequent normal events, it cannot be demonstrably and intelligently purposive, and it is not usually prolonged. The phenomena of epilepsy tend to be episodic, stereotyped, primitive, fragmentary, and unnatural—at variance with usual experience.

Faints and Fits

In a discussion at the Royal Society of Medicine recently it became clear that at times it is impossible to make a sharp division between epilepsy and syncope, although the distinction can nearly always be made for any one attack upon clinical grounds alone. It is probably best to reserve the word "epilepsy" for those cases in which the loss of consciousness is *primarily* due to a cerebral disturbance, and "syncope" for those in which it results *primarily* from a fall in blood pressure. The important qualification here is the word "primarily," for loss of consciousness from either cause may follow disorders of many kinds beyond the range of the present discussion. Whether the *secondary* effect of

the disorder is epileptic or syncopal, the chain of events is in each case relatively constant. The major fit seen in constitutional epilepsy or that symptomatic of bodily disorder is the same in its pattern. Indeed, the nature of the epileptic attack seems to depend more upon the part of the brain affected and the particular brain being affected than upon the causal agent. I have seen volunteers subjected to oxygen intoxication in standard conditions, most of whom had a convulsion at a critical level, but some of whom had an attack of aggressive behaviour—so-called psychomotor epilepsy. The same is true of fainting: the actual sequence of events in the faint is similar whatever the cause.

Syncope may be distinguished from epilepsy often by a cause—postural, emotional, or physical; a fairly long warning, with the characteristic experience, "I feel faint"; protective actions such as sitting; and early onset of pallor, with hot or cold sweating. Consciousness usually returns without any confusion or sequels apart from sweating. The attacks are infrequent. The cerebral anaemia of syncope may lead to a convulsion, but then the primary diagnosis is syncope. Sometimes the two conditions may be very intimately linked, as in the Stokes–Adams attack, in which rapid fall of blood pressure caused by cardiac arrest produces convulsions through cerebral anaemia.

Syncope simulating epilepsy was illustrated by the following case.

A man of 23 had a history of three convulsions. He had had six attacks of loss of consciousness in his life: the first when standing before the blackboard in school; the next after a hearty meal, exhausted from a day's climbing; the next, seeing a crushed thumb dressed; one during a febrile illness with diarrhoea; and two others in tropical weather when standing. In the last three he had had a convulsion, and he said he had been unable to sit down in time to prevent loss of consciousness. He had always suffered from feelings of faintness on rising quickly. He was 6 ft. 2 in. (188 cm.) and only 10½ st. (66.7 kg.), with a pulse rate of 50 to 60, and a diastolic pressure of 55 mm. Hg. The electroencephalogram was normal.

Here, then, was repeated syncope complicated by convulsions, the diagnosis of epilepsy being unjustified. On the other hand there is this case:

A man aged 35 had for six months had attacks of faintness, which had gradually changed their character. They began with fleeting feelings of unreality; then these were accompanied by pallor and goose-skin, later by sweating and the sensation "I feel faint," and finally by a sense of familiarity. Later he lost consciousness in these attacks, which were the result of a malignant glioma arising in the anterior part of his right temporal lobe and invading the lower part of his frontal lobe. This was therefore an example of focal epileptic discharges spreading to a part of the cortex known to bring about modifications in cardiovascular activity, and in consequence causing syncopal changes as part of the epileptic disturbance.

The value of unusual cases of this sort is to emphasize the importance of recognizing the nature of the primary cause of the attack and of basing the diagnosis upon that rather than upon the superficial similarity of the ultimate attack to a fit or a faint.

Forms of Epilepsy

Whatever the cause of the attacks and whatever the electroencephalogram may show, the initial division of the epilepsies is bound to be based on the nature of the observed fit. It so happens that such a division of clinical types of attack is the most useful and fundamental of any, as I hope to show later. It used to be enough to recognize epilepsy, with a division into its major and minor forms, but now more detailed division is essential to the most successful management and treatment of the condition. For instance, minute disturbances of consciousness (petit mal), which are superficially similar, may be caused by slight attacks of each of the different forms of epilepsy, and only most careful observation or questioning may distinguish them from each other.

"Absences"

The French word *absences* immediately calls to mind the frequent petit-mal attacks of childhood. Here there is a brief loss of consciousness, without involuntary movement, sometimes with loss of muscle tone, causing the subject to drop what he is holding, or to fall and as quickly pick himself up. The features of the attack are loss of consciousness and loss of muscle tone. There may be hundreds of attacks a day; they are usually worse in the mornings, and they tend to get less frequent as life advances. They are invariably accompanied by spike-and-wave complexes in the electroencephalogram. These attacks (juvenile petit mal) are accentuated by alkalosis and hypoglycaemia, are not improved by the hydantoins, and rarely improved by sedatives, but respond favourably to the diones and sometimes to such stimulants as caffeine and the amphetamine group of substances.

They may be closely mimicked by other epileptic attacks having a different clinical significance and a different pharmacopoeial response. Very brief clonic attacks with almost imperceptible twitching round an angle of the mouth or in one limb may cause interruption of attention, thought, or consciousness similar to that in juvenile petit mal. Tiny focal sensory attacks may be associated with a similar change; or frontal adversive attacks, in which the head and eyes turn towards one side, may give a similar momentary amnesia. Any evidence of associated disturbance in a patient with brief amnesic attacks should be assessed carefully—muscle-twitching, movements of limbs or eyes, licking, smacking of the lips, a local change in sensation, a fleeting smell or taste, a change in mood, or disturbance of time or reality. Any one of these may lead to the realization that the brief attacks are not juvenile petit mal, with consequent differences in investigations, management, diagnosis, and treatment.

Circumstances in which search for features such as these may be profitable are when the attacks begin after puberty and especially in adult life, when they follow a cause such as a head injury or cerebral disease, when they are infrequent (less than half a dozen a day), when they are less frequent early in the day, or when a number herald the onset of a bigger attack. In these circumstances we may correctly predict that the electroencephalogram will not show the wave-and-spike discharge, and in its absence during a clinical attack the diagnosis of juvenile petit mal may be excluded.

The following are two examples of petit mal—not classical or juvenile petit mal—representing symptomatic epilepsy, and consequently failing to respond to tridione or paradione.

A child aged 13 had had attacks for four years. She might have two in a day or six in a week, but would sometimes be free for two weeks. They occurred at any time of the day. They were stereotyped, and in them she would stop what she was saying or doing, look vacant, mumble for a few moments, go pale, and then resume her activities. She had had meningitis when aged 3 and was the only left-handed member of her family. This, then, was symptomatic epilepsy with transient "purposive" behaviour in speaking—probably a left Sylvian lesion. The electroencephalogram showed abnormality, made up of medium-voltage two- and three-a-second waves with focal spikes in the anterior part of the left temporal lobe. Her attacks had been made worse with tridione.

The second example of symptomatic epilepsy with brief attacks simulating juvenile petit mal was in a 30-year-old woman who for six months had had momentary attacks in which she was amnesic and out of touch with her environment, and in which it transpired that she looked to the left side and sometimes turned her head to that side too. At first she had one every week or two, but they then increased to one or two a day. They were caused by a right frontal glioma which showed as focal slow waves without any "epileptic" discharges in the electroencephalogram.

Attacks with Clonus

Attacks of clonic muscle-jerking have many features in common, whether they are localized to a digit or a limb or involve the whole body. When both sides of the body are involved in a motor fit consciousness is lost except in rare instances. The spasmodic contraction of muscles without regard to their functional relationship that occurs in these attacks is accompanied by very fast waves (spikes) in the electroencephalogram. These may be focal or generalized,

single, in transient bursts, or more prolonged as in a major convulsion. The major convulsion is in fact the ultimate intensity of this form of epileptic discharge. Focal clonus probably indicates a local organic lesion, and when it begins in adult life the possibility should be considered of the lesion being recently acquired. If the attacks change their character progressively the lesion is probably an advancing one. But the pathological nature of the lesion does not alter the fundamental character of the clonic attack. After the causal lesion has been investigated, and if possible recognized, chemical treatment of all attacks with clonus follows the same plan—usually the use of barbiturates and hydantoins.

Attacks with Co-ordinated Movements

There are many attacks in which the movements are smooth and natural, not clonic. Here the epileptic disturbance has arisen in a part of the cortex responsible for co-ordinating and integrating movements. Because of this the cortical discharge causes response in the body which is physiologically integrated, so that, for instance, when muscles contract there is inhibition of antagonists. This is in contrast to the unphysiological simultaneous contraction of agonists and antagonists in the tonic–clonic fit. Because the movement of limbs in these attacks is necessarily co-ordinated, it appears to the observer to be reasonable and to have purpose, although as it is invoked by a primitive epileptic disturbance it is devoid of purpose. Attacks of this sort have been called "psychomotor" or "epileptic equivalents." They are in fact focal epileptic attacks involving cortical association areas, which used to be called silent areas, but which are responsible for the integration of feeling and movement. The movements or feelings which are invoked are consequently more elaborate than in other sorts of attacks. They are commonly seen when a focal fit begins in a temporal or a frontal lobe.

The movements which are seen in these attacks may range from a single act, such as deviation of the eyes, licking, swallowing, or movement of a hand, but they include complicated rituals, salaams, and simple aggressive acts. Most of the prolonged purposive movements seen in association with epilepsy occur in the post-epileptic confusional state, are post-ictal, and are not strictly epileptic.

Post-ictal Activity

It may be difficult to tell when the abnormal behaviour is occurring during the actual epileptic fit (ictal) or after it (post-ictal), particularly when an insignificant and brief fit is followed by a long post-ictal confusional state causing the restless behaviour of a fugue. As a rule the behaviour seen in the fit is apparently spontaneous, and, being the result of the epileptic disturbance of the brain, is stereotyped, short-lived, and without relation to circumstance. The post-ictal activity, whether it is restlessness, aggression, or a fugue, is due to the state of confusion, and so it is simple in its form, evoked by stimulation; when purposeful, primitive, or stupid in its purpose its form is often determined by past experience. It seems automatic. The confused person just walks, or fumbles with clothes, undresses routinely or blindly, resists help or interference. While there can be no real purpose in the ictal activity, any purpose in the post-ictal is immediate and very crude. No prolonged, elaborate, and intelligently purposeful fugue state is epileptic. Very rarely the actual epileptic attack may consist of a lowering of consciousness (confusion) and so simulate the post-epileptic state described in this paragraph.

Sensory Attacks

As sensation must be experienced by the patient there cannot be a sensory equivalent of the major tonic–clonic fit, since consciousness cannot be retained when the epileptic discharge has spread over both hemispheres. The form of sensory disturbance in epilepsy may be negative (loss of sensation) or positive (a hallucination). These may affect common sensation, special senses, or emotions, and mixed forms are common.

The commonest kind of sensory disturbance encountered in epilepsy is very crude—simply tingling at an extremity; but disturbance of proprioception with changes in the shape or position of a limb are met. Epileptic pain is uncommon, but is experienced as a mixture of intense pains, often with a sensation that the limb is in an unnatural position. While tingling is the sensory counterpart of a focal clonic fit, the more complex disorders of feeling, relating to the shape of a limb and causing sensations of bodily or spatial distortion, are the counterpart of the attacks in which co-ordinated movements occur.

Similarly, although when special senses are involved in the epileptic experience they are felt in a most primitive manner—as an unrecognized smell or taste, or flashes of white light—they may be co-ordinated with elaborate formed hallucinations when the epileptic discharge happens to involve one of the special sensory association areas. The most common examples of these are the elaborate, animated, and coloured scenes witnessed by the subjects of lesions in the parieto-occipital area. When even more highly organized areas of cortical integration in the temporal lobes are affected, hallucinations made up of the blending of several sensations may be indivisibly experienced. These may be accompanied by spontaneous and transient emotional disturbances.

The episodic disorders of emotion experienced during temporal lobe attacks have not yet been studied in sufficient detail, perhaps because they are easily overlooked by the questioner, but also because they may suggest to him a psychological disorder rather than a physical disturbance. They may contain any possible emotional experience, any combination of emotions, or any linking of emotion with simpler sensations, and they may evoke appropriate visceral or somatic behaviour. They must be recognized as being epileptic if the patient's problem is to be fully understood.

Prolonged Disorders of Behaviour or Feeling

In status epilepticus, focal or general, abnormal states of movement, sensation, or consciousness may last for many hours. It is usually possible to recognize the individual attacks of the status and so to establish the responsibility of epilepsy for such a prolonged disorder. Otherwise some other cause for the disorder should be sought, since a single epileptic attack is so short-lived. Prolonged amnesic states, fugues, stupor, coma, or aggressive or unsocial behaviour are unlikely to be epileptic in the absence of status, for even post-ictal confusion lasts for minutes rather than hours. In particular, as I have said, activity which is motived, or which uses past learning, cannot be epileptic. The soldier, absent without leave, who finds his way home by road and rail with no memory of the process, could not have done so in an epileptic atack; neither can the criminal who has amnesia for an act of violence directed against a selected subject with an appropriate weapon, however obscure the motive or violent the act. In cases of this sort organic causes having been studied, natural or neurotic motives must be sought, and any evidences of a psychopathic or psychotic personality should be assessed.

It might be said in criticism of this didactic and rigid distinction between epilepsy and other states that the borderland between epilepsy and psychopathy is a narrow one, hardly explored, and that the basis of neither state is understood. That is no justification for a mongrel diagnosis such as that of "epileptoid state" or for the subterfuge of calling inexplicable behaviour epileptic upon tenuous or inappropriate evidence.

A sixth revision of the *Index of Modern Remedies* has been published by the *Scottish Chemist*, 240, Albert Drive, Glasgow, S.1. It includes much information on proprietary preparations and takes note of the 1951 addendum to the *B.P.*, the *National Formulary*, 1952, and the *Pharmacopoea Internationalis*. It is a most useful handbook for all who need an up-to-date guide to modern drugs. The price is 5s., and in London it may be obtained from H. K. Lewis, 136, Gower Street, W.C.1.

ACUTE DISSEMINATED ENCEPHALOMYELITIS TREATED WITH A.C.T.H.

BY

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In 1951 I drew some analogies between the neurological syndromes of serum sickness, polyarteritis nodosa, and acute disseminated and post-exanthematous encephalomyelitis (Miller, 1951). All these conditions show a tendency to gross and often evanescent focal symptoms arising at every level of the nervous system, occasional apoplectic syndromes suggestive of lesions involving major cerebral blood vessels, and pathological changes concentrated in close relation to the cerebral vasculature. It was suggested that some such cases of acute disseminated encephalomyelitis may have their foundation in an allergic vasculitis—an "urticaria of the nervous system"—and trial of cortisone or A.C.T.H. in the treatment of these conditions was suggested.

Although these drugs are known to be without beneficial effect in experimental acute infections of the nervous system of virus origin, such as equine encephalomyelitis and Lansing poliomyelitis (Milzer, 1951), Moyer and his co-workers showed in 1950 that adequate dosage with A.C.T.H. protects effectively against the clinical manifestations of experimental "allergic" encephalomyelitis produced in guinea-pigs by repeated injection of heterologous (rabbit) brain emulsion. Pathological changes in the brains of the protected animals were minimal. Whether such protection is due to inhibition of antibody formation or to a more purely vascular reaction at the site of the lesion (as in inhibition of the Shwartzman phenomenon) is undecided.

Kabat *et al.* (1952) have produced pathological evidence suggesting that the inhibitory effect of cortisone (Kabat *et al.*, 1951) on the development of the similar experimental encephalomyelitis produced in the rhesus monkey by injections of heterologous and homologous brain tissue emulsified with Freund adjuvants (Kabat *et al.*, 1947; Morgan, 1947) is due to suppression of the granulomatous response to the antigenic brain emulsion at the site of injection. It is possible that this local granulomatous reaction is responsible for antibody production; at any rate it appears to be an invariable accompaniment of the development of encephalomyelitis under these experimental conditions (Kabat *et al.*, 1948). Kabat's assumption that the local response plays a causal part in the pathogenesis of the encephalomyelitis is, however, not beyond question: suppression of the neurological illness could be interpreted as a parallel effect of cortisone on hypersensitivity reactions rather than as a secondary result of suppression of the granuloma.

Evidence of the mode of action of cortisone and A.C.T.H. in anaphylactic hypersensitivity in general is somewhat conflicting, and Kabat *et al.* (1952) believe that the balance of such evidence is in favour of inhibition of antibody production as the effective mechanism. In support of this is the observation that whereas these drugs completely or almost completely inhibit the active Shwartzman phenomenon, which depends on the active production of antibody, they are much less effective (if indeed they have any action at all) in inhibiting the passive Shwartzman phenomenon caused by reaction of antigen with antibody already present. In their view the undoubted inhibition of experimental acute disseminated encephalomyelitis by cortisone and A.C.T.H. is probably due "to an alteration in the experimental conditions shown to be necessary for the production of the disease, rather than to any fundamental effect on the disease itself." The pathogenesis of human acute disseminated encephalomyelitis is unknown, and Kabat's view, if correct, provides a further reason for hesitancy in anticipating an effect of cortisone on the human disease analogous to that seen under experimental conditions. Furthermore, should the action of the drug be in fact due to inhibition of antibody production, it is understandable that, even granting the existence of some pathogenetic relationship between experimental allergic and human—for example, post-infective—encephalomyelitis, prophylaxis of the disease in man might be possible but therapy ineffective if the established condition represents a response to antibody already formed at the onset of the illness.

It had previously been shown that some protection against the development of experimental allergic encephalomyelitis was offered by the administration of nitrogen mustard (Koprowski *et al.*, quoted by Moyer *et al.*, 1950) or of salicylates (Good *et al.*, 1949), both of which block antigen-antibody reactions. Antihistamine drugs (Lumsden, 1949) have also been shown to offer some protection against allergic encephalomyelitis in the guinea-pig, though they were without therapeutic effect in the established condition. In this last instance, however, pharmacological evidence would suggest a suppressive action on the "peripheral" pathological expression of an antigen-antibody reaction rather than an inhibition of the reaction itself.

In 1949 Pickar and Kramer reported prompt improvement of a single case of encephalomyelitis following antirabic vaccination (showing a strongly positive skin reaction to the vaccine) after the administration of diphenhydramine hydrochloride.

Glaser and Smith (1951), in reviewing encephalomyelitic syndromes following antirabic therapy, described a fatal case in which 100 mg. of cortisone was given to the patient before he expired. Garrison (1952) reported "dramatic improvement" in a single case of encephalomyelitis complicating antirabies vaccine (phenolized rabbit-brain virus) treated with large doses of cortisone (375 mg. daily for two days, and 100 mg. daily during the subsequent four days). This patient showed great improvement within 24 hours, by which time his high fever subsided. He remained drowsy, however, for four days and retention of urine persisted for six days: five weeks later a single extensor plantar response was the only residual evidence of his illness.

The present paper reports results obtained in a preliminary series of seven cases of acute disseminated encephalomyelitis treated with A.C.T.H. The difficulty of assessing the value of therapy in this disease is evident, as the condition often recovers spontaneously with dramatic suddenness. The results obtained cannot be claimed to be conclusive, but they suggest that the drug may have some value in the therapy of human encephalomyelitis in keeping with its known effectiveness in protecting animals against experimental "allergic" encephalomyelitis.

Selection of Material and Method of Treatment

The material used comprises seven cases clinically diagnosed as acute disseminated encephalomyelitis. All these showed evidence of an acute non-suppurative inflammatory disease of the neuraxis arising in the absence of any relevant neurological past history—except for Case 5, which was regarded as a probable instance of relapsing encephalomyelitis. Tests for syphilitic tuberculous infection of the nervous system were negative in every case, no patient showed recognizable clinical features of infection with the familiar neurotropic viruses, and serological tests for toxoplasmosis were negative in Cases 5 and 7, in which this appeared to be a possible diagnosis. The diagnostic criteria formulated by McAlpine (1931) were found to be of considerable value in assessment. Cases in which there was real doubt about the diagnosis were excluded from the series, as were several patients in whom the diagnosis was clearly correct but who were already showing evidence of spontaneous improvement when they were first seen.

All the patients reported were deteriorating clinically at the time treatment with A.C.T.H. was instituted. The first three cases were treated with A.C.T.H., given by subcutaneous hyalase drip as a measure of economy, but as increasing supplies of the drug became available six-hourly intramuscular injections of 25 mg. were given routinely, augmented by occasional additional injections if a rise in the eosinophil count suggested that 100 mg. daily was physiologically ineffective. Laboratory control was not maintained, however, in the two cases that followed chicken-pox (Cases 2 and 4), which were treated in other hospitals.

The Table summarizes the main features of these cases, which are amplified below.

Summary of Main Features

Case No.	Age in Years	Preceding Infection, etc.	Neurological Syndrome	C.S.F.	Duration of Symptoms at Start of Treatment	Duration of Treatment in Days	Total Dosage of A.C.T.H. (mg.)	Control by Eosinophil Counts	Progress after Institution of Treatment with A.C.T.H.
1	22	Respiratory illness	Transverse myelitis	Normal	42 hours	5	200	+	Apparently dramatic response. Rapid and complete recovery
2	6	Varicella	Stupor, flaccid quadriparesis, ataxia	,,	5 days	4	125	0	No dramatic response. Good recovery within four days
3	31	Chilling only	Transverse myelitis, with some drowsiness	,,	12 ,,	7	700	+	Improvement within 12 hours. Fair recovery
4	6	Varicella	Coma, meningism	Mixed pleocytosis (16 cells)	48 hours	3	300	0	Deterioration during first 13 hours. Improvement began after 36 hours. Complete recovery in seven days
5	14	Fifth post-coryzal episode of apparent recurrent encephalomyelitis	Stupor, cerebellar syndrome, diplopia	Normal	12 ,,	1	100	+	Improvement within six hours. Complete recovery in seven days
6	30	Nil	Severe ascending myelitis, with meningism	1. Normal 2. Mixed pleocytosis (36 cells)	19 days 28 ,,	8 5	560 575	0 +	Great deterioration Slight deterioration
7	12	(Brother of Case 5) Coryza	Stupor, cerebellar syndrome	Normal	15 hours	3	325	+	Improvement within 12 hours. Complete recovery in three days

Case 1

Transverse myelitis developing after acute respiratory illness. Treatment with A.C.T.H. began within 42 hours of onset. Apparent improvement within one and a half hours of first injection. Transient increase of disability 36 hours after beginning treatment was associated with a rise in the eosinophil count, and continued improvement rapidly followed an increase in dosage. 200 mg. of A.C.T.H. was given in a hyalase drip over five days, and complete recovery occurred in seven days.

On October 24, 1951, a 22-year-old medical student developed an acute respiratory illness of a type which was common in his neighbourhood at the time. This began with 24 hours of laryngitis followed by fever and cough. He became short of breath and developed moist sounds at both lung bases and in the right axilla. He was given penicillin and sulphonamides by his doctor, and although his evening temperature remained between 99 and 100° F. (37.2 and 37.8° C.), his condition was improved on the fourth day. On the night of the fifth day, however, he was awakened from sleep by severe pain in the small of the back. The pain was chiefly in the muscles, more severe on the right than the left, and it was so intense in every position that it prevented sleep after the onset. Next morning the pain was still intense, and by the afternoon of the following day (sixth day of illness) he found some difficulty in raising himself from the bed.

Examination on the evening of the same day revealed a temperature of 101.5° F. (38.6° C.), tenderness of the quadratus muscles, and weak flexion of the back and hips. There were no reflex or sensory changes, but the story was highly suggestive of a developing myelitis, and he was admitted to hospital. Later that night the plantar responses became equivocal and pronounced dysuria developed. The next morning (seventh day of the illness) he had developed severe weakness of both legs and bilateral partial foot-drop, with extensor plantar responses; micturition had become so difficult that manual pressure on the bladder was required. By the afternoon of the same day the back pain was less intense but weakness of the legs and back more profound, and micturition more difficult. Arrangements were made for catheterization and tidal drainage, but again the bladder was emptied successfully by manual compression. There was no headache or meningism, and the spinal fluid was normal in pressure and composition.

At 6 p.m. on the seventh day, 42 hours after the onset of neurological symptoms, he was given 10 mg. of A.C.T.H. intramuscularly, and a subcutaneous drip containing 20 mg. of A.C.T.H., 1,000 units of hyalase, and 250,000 units of penicillin was given via the soft tissues of the thigh. At this stage the eosinophil count was 309 per c.mm. The patient described great subjective improvement within 90 minutes of the initial intramuscular injection. For the first time in 21 hours he passed urine without difficulty; he also claimed some improvement of power in the legs, which could not be objectively confirmed.

During the next 24 hours the patient was given the 20 mg. of A.C.T.H. in the initial hyalase drip, and he again claimed improvement in his general condition and in the power of his legs. His eosinophil count, however, had dropped only to 206 per c.mm., and next morning (ninth day of illness), when a second similar drip had been running for 12 hours, he once more found difficulty in micturition. The eosinophil count at this time was 211 per c.mm., and in view of the failure to obtain a better reduction it was felt that dosage was physiologically inadequate. The drip was therefore continued, but a further boosting dose of 10 mg. of A.C.T.H.

was given. Within four hours he was again passing urine normally and the eosinophil count had fallen to 92 per c.mm. The strength of the subcutaneous drip was therefore doubled. It now contained 40 mg. of A.C.T.H. in the pint (570 ml.), and this amount, given every 24 hours during the next three days, succeeded in bringing the eosinophil count down to between nil and 6 per c.mm.

From the time of the second boosting dose there was no further difficulty with the bladder, and improvement was progressive and remarkably rapid. By the morning of the tenth day there was a striking objective improvement in the motor power of the legs and the patient could easily sit up unaided. The plantar responses, which the previous day had been clearly extensor, became equivocal, and on the morning of the eleventh day they were flexor, and remained so. When the drip was dismantled, 72 hours after the second boosting dose was given, there was no muscular weakness or abnormal physical signs. The temperature had become normal within 12 hours of the starting of treatment, and by the time treatment was discontinued the E.S.R. had fallen from 42 to 34 mm.

On the thirteenth day of the illness the patient was allowed out of bed and walked the length of the ward without difficulty. However, he had some pain in the back during the following night, and he was therefore kept in bed for a further three days, during which time his sole complaint was of some nocturnal discomfort in the back. By the seventeenth day these symptoms had entirely disappeared, and his E.S.R. had fallen to 20 mm. in the hour. He was able to walk without difficulty and was discharged to his home.

Convalescence was uneventful, the only residual symptoms being occasional backache and some stiffness and pain in the muscles of the left calf and thigh. These symptoms disappeared completely within three weeks, and there has been no subsequent disability of any kind.

Case 2

Encephalitic illness with flaccid quadriparesis beginning in a child of 6 five days after the appearance of chicken-pox. Treatment was started five days after the onset of symptoms and 25 mg. of A.C.T.H. was given daily by hyalase drip during the subsequent three days. During this time there was only slight improvement. On the last day of treatment the strength of the drip was doubled, and during this period of 24 hours, in which she was given 50 mg. of A.C.T.H., rapid and complete recovery occurred.

Ten days before admission to hospital this 6-year-old girl developed a typical chicken-pox rash and was well in herself within 48 hours of its onset. Five days before admission, however, she stopped eating, complained of feeling generally unwell, went spontaneously to bed, and slept a great deal during the day as well as at night. Two days before admission she became unsteady on her feet and with her hands, weak in all her limbs, drowsy, and apathetic. She complained of severe headache and had much difficulty in micturition.

Examination on admission revealed no fever, neck stiffness, or abnormal signs in the cranial nerves. The pupils and optic fundi were normal and there was no nystagmus. The child was stuporous, answered questions with great difficulty, and was grossly ataxic. She could not sit up, though she could place her two forefingers together with fair accuracy. The limbs were completely flaccid and the deep reflexes profoundly depressed symmetrically. The plantar responses were extensor. There was no family history of tuberculosis, or any preceding history of relevant disease, the Mantoux reaction was negative, and the spinal fluid entirely normal in pressure and composition. The initial eosinophil count was only 12.5 per c.mm,, and in view of this initial low level it was not possible to assess the physiological adequacy of A.C.T.H. dosage by serial counts.

At 7 p.m. on the day of admission to hospital (ten days after the appearance of the chicken-pox rash and five days after the onset of symptoms), a hyalase drip was given by way of the soft tissues of the thigh, and during each of the next three periods of 24 hours she received a pint (570 ml.) of saline containing 25 mg. of A.C.T.H., 1,000 units of hyalase, and 250,000 units of penicillin. There was no dramatic improvement. On re-examination after three days' treatment she was more easily roused and more willing to talk, the hypotonia was less profound, and there was some improvement in muscular power, but the deep reflexes and plantar responses were unchanged.

In view of the absence of any clear response and of the impossibility of assessing whether a physiologically effective dose was being given, it was decided to discontinue treatment. During the next 24 hours, however, the remaining allotment of A.C.T.H. for this patient (50 mg.) was given in the form of a hyalase drip twice the strength of those previously administered.

During this 24 hours she showed much improvement, and at the end of this period she could sit up, take food, and talk freely. The deep reflexes were still sluggish, but the plantar responses had become flexor. Improvement was maintained, and on the next day she was reading comics and was able to get out of bed and play in the room. Ten days later she was discharged without symptoms or residual physical signs, and her health has since been excellent.

Case 3

Transverse myelitis of gradual onset, with some impairment of consciousness, after chilling in a man aged 31. Treatment was begun 12 days after the onset of symptoms, and during the subsequent seven days 700 mg. of A.C.T.H. was given. There was appreciable improvement within 12 hours, and this was continued. On conclusion of treatment spastic paraplegia remained, and slow improvement has occurred during subsequent months.

Thirteen days before admission to hospital this 31-year-old man was working as an erector on a high building in very cold weather. The next morning he awoke feeling miserable and had a weary sensation in his legs. These symptoms persisted during three days at work, and on the fourth day of the illness severe pain occurred in both legs and he found it difficult to cycle home. He stayed in bed and was seen by his doctor two days later. On this, the sixth day of the illness, he became very drowsy, and the pain in the legs spread up to the lumbar region. Two days later, however, he felt better and got out of bed to see the doctor; he found, however, that his legs were so weak that he could not walk for more than 20 yards, so he returned to bed. During the next five days his condition deteriorated. Severe back pain continued and there was progressive weakness of the legs, which twitched a good deal during the night. From the tenth day of the illness he noticed increasing difficulty in passing urine.

On admission to hospital on the twelfth day of his symptoms he was drowsy, but gave an excellent history when roused. There was no neck stiffness or fever. The abnormal findings in the nervous system were spastic weakness of the right arm with increased reflexes, symmetrical absence of the abdominal responses, spastic weakness of both legs, more pronounced on the left, with exaggerated knee-jerks and ankle clonus. The plantar responses were bilaterally extensor and a crossed extensor reflex was obtained on both sides. There was profound impairment of superficial sensation below and including the eighth thoracic dermatome. Vibration sense was intact, but muscle-joint sense was greatly impaired peripherally, and the patient stated that while he was quietly lying in bed the legs felt as though they were dangling over the side. He could hardly move the left leg at all, and could raise the right knee only a few inches from the bed. He could not dorsiflex the left foot, and this movement was weak on the right. Spinal fluid was entirely normal, and the blood eosinophil count was 180 per c.mm.

A subcutaneous drip containing 40 mg. of A.C.T.H., 1,000 units of hyalase, and 250,000 units of penicillin was given

through the soft tissues of the thigh. Twelve hours later the eosinophil count had dropped to 50 per c.mm. and there was a striking improvement in the patient's clinical condition. Consciousness was clear, and, although reflex changes were as before and there was no alteration in sensory level, all movements of the right leg were greatly improved and power in the left leg was as good as that in the right leg had been the previous evening.

On the second day of treatment the patient stated that the lower part of his body felt less numb, but there was no objective sensory improvement. Dysuria was no longer present and spontaneous twitching of the legs had ceased. He was now able to perform isolated movements of the toes of the right foot, and the crossed extensor response was no longer obtainable on either side. However, his eosinophil count had risen to 200 per c.mm., although two intramuscular boosting doses each of 20 mg. of A.C.T.H. had been given during the course of each day, raising the actual total daily dosage to 80 mg. during the first 48 hours. In view of the doubtful physiological response the hyalase drip was abandoned at the end of this period, and during the subsequent five days the patient was given 100 mg. of A.C.T.H. daily in six-hourly doses of 25 mg. each, and his eosinophil count remained in the region of 20.

During these five days improvement was rapid. On the fourth day of treatment (second day of full dosage) deep reflexes in the right arm were normal and all movements of the legs had improved. On the sixth day of treatment there was shrinkage of the area of sensory loss from above and below.

Improvement continued after completion of the course of A.C.T.H. There was one brief setback on the fourth day after treatment was abandoned, during which the patient complained of drowsiness, some increased difficulty in using the legs, and an increase of numbness on the front of both thighs. However, the next day improvement continued spontaneously.

Seven days after the completion of treatment leg movements were full but weak, and the patient could hoist himself into a sitting position with his legs over the side of the bed, though they were not yet strong enough to support the weight of the body unaided. Muscle-joint sense had returned completely, and superficial sensory loss was limited to symmetrical areas over the second lumbar dermatome. Abdominal responses remained absent, knee- and ankle-jerks were overbrisk, and the plantar responses were extensor.

Three months after the illness the findings were those of a featureless spastic paraplegia of mild degree without sensory change, and the patient could walk well with the aid of sticks.

Case 4

Severe encephalitic illness with coma, meningism, involuntary movements, disappearance of deep reflexes, extensor plantar responses, and spinal-fluid changes beginning in a 6-year-old child five days after appearance of chicken-pox. Treatment with A.C.T.H. was begun within 48 hours of the onset of symptoms, and 300 mg. of A.C.T.H. was given during the subsequent 72 hours. Deterioration occurred during the first 15 hours of treatment, but improvement was noticeable 24 hours later and was progressive from this time, with perfect recovery except for emotional lability nine days after the onset.

Seven days before admission to hospital this 6-year-old boy had a typical chicken-pox rash. Five days later, when the rash was fading, he developed frontal headache and drowsiness; and during the subsequent 48 hours headache persisted, drowsiness increased, and he became restless, confused, and quite oblivious of his surroundings.

On admission two days after the appearance of nervous symptoms he was mute and restless, and there were violent non-purposive movements of all limbs. He had severe neck stiffness and almost continuous irregular involuntary movements of the eyes, with periods of several seconds during which they remained fixed upwards and convergent. He was doubly incontinent, and the temperature was 99° F. (37.2° C.). Judging from his violent responses to gentle stimulation there appeared to be general skin hyperaesthesia. The knee- and ankle-jerks were sluggish, the abdominal reflexes and cremasterics brisk, and the plantar responses clearly extensor. There was no true nystagmus, and the optic fundi were normal. The spinal fluid showed a normal protein content but contained 16 cells per c.mm., 10 of which were polymorphonuclear leucocytes. He was given an immediate injection of 25 mg. of A.C.T.H., and during the next 72 hours received 300 mg. in all by similar six-hourly intramuscular injections. The dosage was not controlled by eosinophil counts.

On re-examination 15 hours after the first injection (after the administration of 75 mg. of A.C.T.H.) the child's condition had deteriorated. Stupor had deepened to coma, and he was quite unresponsive. The abdominal reflexes had disappeared, though the cremasterics were retained, and neither knee- nor ankle-jerks could be obtained. There was involuntary and continuous twitching of the eyelids and of the right angle of the mouth. Otherwise the signs were unchanged, except that the involuntary ocular movements previously described were more persistent and more violent.

On examination 24 hours later there was some improvement. Coma alternated with episodes of extreme restlessness and the child screamed on lumbar puncture, which now yielded 20 cells per c.mm. Polymorphonuclear leucocytes still predominated and the protein content remained normal. Neck stiffness was less severe, and the ocular movements and facial twitching were less continuous. Within the next 24 hours pronounced improvement occurred, stupor giving place to the picture of cerebral irritation, and at the end of this time (63 hours after the beginning of treatment) neck stiffness had disappeared, the child looked round when his name was called, and he followed the nurse round the room with his eyes. He was still mute and doubly incontinent, but now responded violently to subcutaneous injection. He was very restless and was moving his legs, which had previously been quite still, though reflex signs remained unchanged.

This improvement was maintained. Twenty-four hours after completion of treatment (seventh day of illness) he spoke a little and was intermittently rational. The reflex signs of an upper motor neurone lesion faded, the gross general ataxia which became evident during recovery gradually disappeared, and sphincter control returned. Four days after completion of treatment there was no residual disability. The child was somewhat labile emotionally, the knee- and ankle-jerks remained absent, but all other signs had disappeared and he was perfectly well. He had little memory for the illness of the preceding ten days. Improvement after this time was continuous, and within three weeks the child was apparently normal.

Case 5

A.C.T.H. treatment of the fifth encephalitic illness occurring in a boy of 14 during the course of five months. Each episode followed an upper respiratory infection, and the usual clinical features were drowsiness, meningism, nystagmus, hypotonia, and disappearance of deep reflexes with extensor plantar responses. Treatment began 12 hours after the onset of the fifth attack. Improvement was evident within six hours of the starting of treatment, and in 18 hours the patient was well except for nystagmus, which disappeared within seven days.

In July, 1951, a 14-year-old boy had a minor head injury. He received a blow on the left parietal region and was dazed for two hours. There was a haematoma at the site of injury, but there were no abnormal neurological signs, the *x*-ray film of the skull was negative, headache disappeared within three days, and the patient returned to school two weeks later without symptoms.

In November, 1951, he had a severe head cold with fever, cough, and sore throat. Ten days after the onset, when his respiratory symptoms had almost disappeared, he became drowsy, with meningism, retention of urine, disappearance

of deep reflexes, nystagmus, hypotonia, and ataxia. The superficial reflexes disappeared, and the plantar responses became extensor. He was stuporous for ten days before recovery began. Diplopia and nystagmus subsided in two weeks, and on discharge from hospital a month after the onset of the illness his symptoms and signs had completely disappeared.

Two months later, in January, 1952, a similar illness with identical symptoms and signs followed a further head cold. On this occasion recovery was more rapid; consciousness was clear within five days of the onset and the patient asymptomatic five days later without residual physical signs.

A month later sore throat without coryzal symptoms was followed by a similar illness. On this occasion diplopia was localized to a paresis of the right internal rectus. All ancillary investigations were negative except that an electroencephalogram showed gross abnormality (generalized asynchronous theta and delta activity with a focus of delta waves in the right posterior temporal region). Consciousness was clear within five days, double vision and nystagmus again cleared a week later, and at this time the patient was well once more.

The fourth episode occurred in March, 1952, after a severe head cold. Abnormal signs were as before. On this occasion the neurological illness was more prolonged and the patient was unrousable for eight days. Four specimens of spinal fluid were normal, and the fifth showed nine lymphocytes per c.mm. as the only change. The electroencephalogram again showed evidence of diffuse disturbance of cerebral function, but the focus in the right temporal region was less clearly defined. Complete recovery occurred within 16 days of the onset, and a week later the electroencephalogram was much more normal, showing merely a well-sustained alpha rhythm interspersed with diffuse theta activity.

He was readmitted in May, 1952 (two months after the fourth episode), having had a heavy coryza for four days. He retired to bed the day before admission quite well except for his cold, but awoke at midnight mentally confused, restless, ataxic, and with marked difficulty in micturition. In the morning he was stuporous, with double vision, gross nystagmus in all directions, hypotonia, ataxia of limbs and trunk, disappearance of all deep reflexes, and flexor plantar responses. The spinal fluid was normal.

Twelve hours after the onset of this episode 25 mg. of A.C.T.H. was given by intramuscular injection, and this was repeated three times in the next 24 hours. Within six hours the patient was less drowsy and nystagmus in all directions less gross. Improvement was progressive, and 18 hours after the beginning of treatment consciousness was normal and all signs had disappeared except for fine nystagmus in all directions and sluggishness of the deep reflexes. No further A.C.T.H. was given: improvement was progressive, and nystagmus finally disappeared on the seventh day. As in the previous episode, electroencephalographic changes indicating a severe disturbance of cortical metabolism (generalized asynchronous delta activity) gave place to a more normal record as the symptoms subsided.

Ancillary investigations in this case included culture of the spinal fluid and its injection into the brains of mice and guinea-pigs without pathological result. Serological tests for toxoplasmosis, cold agglutinins, and heterophil antibodies, and biopsy of one of a group of enlarged cervical glands all failed to reveal any evidence of specific disease. All ancillary general medical investigations, including serological tests for general infections, Mantoux tests, extensive radiological examinations, including air-encephalograms, were negative. Arrangements were made for cerebral angiography, but these were abandoned when the patient's brother (Case 7) developed a similar illness after an upper respiratory infection.

Case 6

Severe subacute ascending myelitis in a 30-year-old woman with an episode of meningism one month after the onset. Deterioration occurred during an initial (uncontrolled) course of A.C.T.H., and there was further slight deterioration during a second course of treatment in the meningitic phase.

A 30-year-old housewife was well until April 11, 1952, when she developed unpleasant tingling under the left breast which lasted for a week, and was followed by progressive numbness of the left leg and left side of the trunk. Within a few days the right foot became numb and cold, numbness spread upward to the right leg and trunk, and stiffness of the legs developed with increasing dysuria.

When she was admitted to another hospital on May 1, examination revealed a flaccid paraplegia with paralysis of the left leg, absent abdominal responses, increased knee- and ankle-jerks, flexor plantars, and marked impairment of all forms of sensation below the fifth thoracic dermatome. The spinal fluid dynamics and composition were normal, and there were no signs above the upper level of sensory loss. From May 1 to 6 she was given 80 mg. of A.C.T.H. daily in four intramuscular injections, and during the next two days 40 mg. daily in two doses. Dosage was uncontrolled by eosinophil counts. During this course her condition became much worse. On the third day of treatment weakness of the right leg became absolute, with complete loss of sensation below T 5 and retention of urine. Ancillary tests were entirely negative.

The patient was admitted to the Royal Victoria Infirmary on May 9. Her signs at this time were of an apparently complete cord lesion, the upper level of which had ascended to T 3, with a zone of hyperaesthesia at T 2. Below this level there was complete sensory loss and disappearance of all reflex activity. For 24 hours before admission she had complained of shooting pain down both arms and of severe headache which was associated with meningism. Re-examination of the spinal fluid showed normal dynamics and protein content, with 36 cells per c.mm., 11 of which were polymorphonuclear leucocytes. It was felt that this was a case of ascending and possibly necrotic myelitis which had clearly not shown any response to A.C.T.H. in dosage probably physiologically adequate though uncontrolled. The chances of the cord lesion responding to treatment appeared remote, but, in view of the onset of meningism and the clinical evidence of upward extension of the spinal lesion, a further course of A.C.T.H. was given in the hope of averting respiratory failure or an encephalitic illness.

During the subsequent five days she was given 100 mg. of A.C.T.H. daily and the eosinophil count was maintained below 10 cells per c.mm., with the addition of occasional boosting doses. She received 575 mg. of A.C.T.H. in all.

During the first four days of treatment her condition showed slight deterioration. Grip in both hands became weak and the deep reflexes in the arm, previously brisk, were elicited with difficulty and finally disappeared. Neck stiffness and headache remained as before. On the fifth day she developed a high fever with pyuria and basal pneumonic signs. In view of this, treatment with A.C.T.H. was abandoned. The fever and these infective signs responded to antibiotics, and meningism disappeared 40 hours after A.C.T.H. was discontinued.

During the next two months there was no change in the neurological signs. Retention of urine remained complete, and there was no recovery of sensation, motor power, or reflex activity, or any evidence of extension of the lesion.

Case 7

Acute encephalitic illness with cerebellar symptoms following an upper respiratory infection in a boy of 12. Treatment with A.C.T.H. began within 15 hours of the onset and improvement was evident 12 hours later. 325 mg. of A.C.T.H. was given during the course of 72 hours, with complete recovery except for minor residual signs.

This patient, a 12-year-old boy, is the younger brother of Case 5. On May 19, 1952, seven months after the onset of his brother's illness, and six days after the elder boy's fifth encephalitic episode, described above, he developed a syndrome closely similar in type.

Two years previously this boy had sustained a fractured skull, with transient loss of consciousness, but he made an excellent recovery and had no subsequent symptoms except for occasional headaches and rather unruly difficult behaviour of doubtful significance.

On the morning of May 19, at which time he was recovering from a severe head cold contracted one week previously, he awoke complaining of dizziness, headache, and double vision on looking to either side. He fainted on endeavouring to leave his bed, and within six hours of the onset became drowsy, though he could be roused.

On examination 15 hours after the onset he was stuporous but talked sensibly on being wakened. He complained of occipital headache, double vision, and giddiness on raising his head from the pillow. The positive signs on examination were meningism, gross nystagmus which was present in all positions of the eyes and maximal on lateral deviation, gross generalized hypotonia, sluggish deep reflexes in the arms, and almost extinct knee- and ankle-jerks. The plantar responses were flexor and the abdominal reflexes tired easily. The spinal fluid was entirely normal and the electroencephalogram showed diffuse theta activity with paroxysmal bursts of higher amplitude but no evidence of a focal lesion.

The boy was given 50 mg. of A.C.T.H. intramuscularly on admission and 25 mg. six-hourly during the subsequent 72 hours. Twelve hours after treatment started he was more alert, nystagmus was less sustained, and the right ankle-jerk was easily obtained. Re-examination 36 hours after the onset of treatment showed complete disappearance of meningism and nystagmus. Diplopia had disappeared, headache was the sole subjective complaint, and reflex changes were as before.

On completion of treatment there were no symptoms, and the only abnormal signs were sluggish knee- and ankle-jerks. Hypotonia had completely disappeared. Ancillary investigations were entirely negative.

Discussion

The hypothesis on which this therapeutic experiment is based is that the clinical syndrome of acute disseminated encephalomyelitis in man may arise on the basis of vascular and perivascular changes in the nervous system which are interpreted as pathological expressions of a non-specific hypersensitivity reaction of anaphylactic type, probably primarily vascular but involving, either simultaneously or secondarily, the extravascular mesenchymal tissues of the neuraxis. Some hope that the disease in man might be influenced by cortisone or A.C.T.H. is offered by the observations that these drugs exercise a powerful prophylactic effect on experimental "allergic" encephalomyelitis, which is in some ways strikingly similar to the human disease; and that they suppress the established general manifestations of serum sickness—a frank expression of hypersensitivity which may rarely be complicated by an encephalomyelitic syndrome.

Even if theoretical and practical objections to this hypothesis prove invalid, and it is ultimately shown to be an approximation to the truth, the limitations of its therapeutic application are at once apparent. The most that could be hoped for on theoretical grounds is that physiologically effective dosage of cortisone or A.C.T.H. might diminish the inflammatory response by decreasing or abolishing exudation from damaged blood vessels, and might possibly accelerate the absorption of exudate and the resolution of inflammatory change which presumably occur during spontaneous recovery. This implies two practical limitations: first, that the drug would be likely to influence the condition only during the phase of exudation and acute inflammation; and, secondly, according to this hypothesis the focal and general neurological symptoms of encephalomyelitis arise from damage to neurones and their processes by oedema, haemorrhage, or toxic substances essentially secondary to vascular-mesenchymal inflammation: any detectable clinical response to therapy could at best be anticipated only in relation to symptoms arising from neural lesions not already irreversible by reason of their duration or their initial severity. Even on theoretical grounds no response would be expected, for example, in the rapidly fatal encephalomyelitic illness of which the pathological basis is a diffuse cerebral purpura, or in those cases of severe myelitis which are characterized by actual necrosis of the spinal cord.

Critical consideration of the present small series of cases does nothing to invalidate these theoretical views, and offers a small amount of admittedly fragmentary clinical evidence in their support.

The mortality of encephalomyelitic cases admitted to the Royal Victoria Infirmary is in the region of 27% (8 of 30 cases occurring between 1930 and 1940), and somewhat similar figures are reported by most other observers. Certainly in "spontaneous" cases and in those following Jennerian vaccination, and probably in post-exanthematous instances, fatalities occur almost entirely among patients in whom coma is a clinical feature. Only one of the present patients, however (Case 4, following chicken-pox), was ever more than stuporous, and although this was an unusually severe illness, encephalomyelitis following varicella is widely regarded as having a rather better prognosis than similar illnesses following some other exanthemata such as measles. The absence of fatalities in the present series is therefore valueless in the assessment of treatment.

In one case (Case 6, subacute ascending and probably necrotic myelitis) treatment with A.C.T.H. clearly exerted no beneficial effect: unequivocal clinical deterioration occurred during both an initial uncontrolled and later a controlled course of treatment.

In neither of the instances of encephalomyelitis following chicken-pox (Cases 2 and 4) was the course or duration of the illness materially different from that which is often seen in untreated cases, though the improvement which coincided with increased dosage in Case 2, and that which followed an initial phase of deterioration in the much more severe Case 4, are compatible with the view that the drug exercised a favourable effect on the condition.

In Cases 5 and 7, clinical improvement was evident within six and twelve hours of the initial injection of A.C.T.H. respectively, and a similar response has since been observed in a sixth encephalitic episode in the former case that is not detailed here. Unfortunately the previous history of cerebral trauma in both these cases, as well as the remarkable familial incidence, renders diagnosis ultimately problematical. Cases of relapse and recurrence of encephalomyelitis are not rare, and several have been personally observed, though never with so many attacks as have been seen in Case 5. However, the encephalitic nature of the syndrome with a maximal though not exclusive incidence on the cerebellum or its connexions, its relation to preceding banal infection, its rapid and complete resolution clinically and electroencephalographically, and the absence of spinal-fluid changes, would appear to render any diagnosis other than acute disseminated encephalomyelitis difficult to sustain.

In Case 3 the improvement in mental acuity and in the clinical manifestations of the transverse cord lesion which was observed within 12 hours of the first injection is surprising, even on theoretical grounds, in view of the 12-day history of the condition. It should be noted, however, that this patient was still deteriorating clinically when treatment began, which presumably argues a continuing inflammatory reaction in the nervous system, and that he was left with appreciable disability, in keeping with the duration of his cord lesion. The slight relapse which occurred four days after completion of treatment is perhaps also a point in favour of the view that A.C.T.H. may have exercised a suppressive effect on the symptoms in this case.

These cases are numbered in the order in which they were treated, and it is ironical that the evidence in favour of a therapeutic response is more suggestive in Case 1 than in any subsequent patient. In this instance a combination of

circumstances—in particular an intelligent patient and a very alert practitioner—led to reference of the case at a much earlier stage in the development of the disease than is usual. Although clinical deterioration until treatment was instituted was rapidly progressive, it is clearly impossible to claim with any certainty that the apparent response was more than coincidental. Nevertheless the relapse associated with objective evidence of physiologically inadequate dosage, and the resumption of improvement when dosage was increased, as well as the remarkably complete recovery which was evident within a matter of days, render coincidence a not entirely satisfying explanation: that resolution of the condition was related to the administration of A.C.T.H. would appear to be a distinct possibility.

Acute disseminated encephalomyelitis is a rare disease, and, although it is fully appreciated that no firm conclusions can be drawn from the present small series of treated cases, they are reported in the belief that the results are suggestive enough to merit similar trial on a larger scale. In the absence of any other effective or rational therapy such a trial would appear justifiable, though a word of caution is advisable. Diagnosis of acute encephalomyelitis following exanthemata is usually simple, but the "spontaneous" examples, and those following non-specific infections, may present difficult diagnostic problems. Administration of A.C.T.H. to cases of virus disease such as poliomyelitis is at best useless, and recent evidence suggests that it may be actively harmful. In bacterial infections such as cerebral abscess or tuberculous meningitis its use might well be disastrous. For these reasons, and also in order not to confuse assessment of the value of the drug in the disease under consideration, the employment of this experimental therapy should be limited to cases of acute neurological illness in which an unequivocal diagnosis of encephalomyelitis can be competently sustained. The present paper shows that in such cases the drug is harmless if nothing more.

Summary

Seven cases clinically diagnosed as acute disseminated encephalomyelitis have been treated with A.C.T.H. They comprise two cases of encephalomyelitis following varicella, two cases of transverse and one case of subacute ascending myelitis, and two (familial) cases of encephalitic illness following non-specific infection, in one of which there have been recurrent encephalitic illnesses. Acute disseminated encephalomyelitis has a pronounced tendency to rapid, spontaneous, and often complete recovery, and no final conclusions regarding the efficacy or otherwise of A.C.T.H. can be reached without extended observations on a scale which would permit of statistical evaluation. It is believed that the results reported here are suggestive enough to justify further trial.

I wish to thank practitioners and consultants in Region No. 1 who have been kind enough to refer cases for treatment, Dr. G. A. Smart for help and advice on technical aspects of the use of A.C.T.H., and Dr. M. J. Evans for his clinical assistance.

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ANURIA TREATED BY CORTISONE*

BY

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The present trend in the treatment of anuria is in favour of a conservative policy using a balanced fluid and electrolyte intake with a low-protein diet in the hope of a spontaneous remission (Bull *et al.*, 1949). In cases in which gross oedema or some electrolyte imbalance has already occurred active measures to substitute for the kidney must be used.

Methods of treatment based on the primary aetiology, such as decortication, nerve block (surgical or pharmacological), alkalization of the urine, etc., are not often successful. This relative failure may be due to the presence of other unsuspected aetiological mechanisms. The possibility that an acute allergic reaction in the kidneys is a causal factor in some cases is considered in this communication. To test this hypothesis we have tried the effect of cortisone in a miscellaneous group of four cases of anuria. The cortisone used was cortisone acetate ("cortone"), and was given by intramuscular injection, except where oral administration was specified.

Case 1

A man aged 33 was admitted to the Mater Misericordiae Hospital on October 27, 1950, suffering from rheumatoid arthritis, grade II, of ten years' standing. The previous history was irrelevant. There were four areas of alopecia areata on the scalp. His general physical examination was otherwise normal, but the urine contained a very faint trace of albumin, a few squamous cells, and a very rare leucocyte. The electrocardiogram was normal; the blood pressure was 140/80; and the E.S.R. 45 mm. (1 hour). Seven days after admission he was started on cortisone treatment. By November 30 the arthritis had improved by 80%, and cortisone was discontinued on November 26.

By December 1 a relapse of the arthritis was evident and cortisone treatment was resumed: 100 mg. a day orally, in three doses, was given, and because of a favourable response it was reduced to 50 mg. on December 5. As, however, a considerable amount of fluid had developed in the left knee, the dose was increased to 100 mg. a day by mouth on December 13. On December 15 the patient returned home on this dosage, and on the 24th he developed acute pharyngitis with pyrexia of 101° F. (38.3° C.), and was treated with penicillin. Some hours later there was a transient erythematous rash on the trunk. On December 25, contrary to instructions, he ceased taking cortisone; next

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day he had almost complete anuria, passing only about 1 oz. (28 ml.) of urine during 24 hours. He was readmitted to hospital on December 26 by Dr. Jacob Robinson.

From time of readmission to December 27 inclusive he passed no urine, his temperature was about normal, but his pulse rate varied from about 100 to 120 a minute, and the respiratory rate from 38 to 50; he had a moderate amount of general oedema, which increased daily. On December 28, 15 ml. of urine was obtained by catheter; it was acid in reaction, contained +1 albumin, a few epithelial cells, a rare leucocyte, and *a very rare erythrocyte*, but no casts or bacteria. On the same day his blood urea was 210 mg. per 100 ml. Some fine crepitations were heard over both pulmonary bases, and an *x*-ray film of the lungs (portable apparatus) seemed to show a small area of consolidation at the base of the right lung, with a small pleural effusion at the left costophrenic angle. His blood pressure was 142/90 and varied little from this figure throughout the whole period of observation. Because of nausea he took nothing by mouth except a little fluid.

As the patient was seriously ill, in addition to the usual therapeutic measures peritoneal lavage by drip with alternating normal saline, Hartmann's solution, and glucose–saline was given by Mr. J. F. O'Sullivan and Dr. M. I. Drury; after this procedure had gone on for some hours the lavage fluid showed 90 mg. of urea per 100 ml. Procaine was also tried by intravenous drip, and antazoline by mouth. Next day (December 29) the patient's condition was much worse, the general oedema had increased, he was semi-conscious, nausea was intense, and the respiratory rate averaged 50 a minute. The pupils were not contracted and retinoscopy revealed no abnormality; 210 ml. of urine was obtained by catheter and showed +1 albumin, numerous squamous cells and leucocytes, a moderate number of erythrocytes, and a few granular casts.

On December 30 his general condition was so bad that the outlook appeared hopeless. The general oedema had increased, the respiratory rate was 40 a minute, with air hunger, and the blood urea was 240 mg. per 100 ml. By catheter we obtained 360 ml. of urine, which showed +2 albumin with a moderate number of erythrocytes and an increase in the number of granular casts. The plasma CO_2-combining power was down to 18 vols.%. On December 31 the position was so grave that it was decided to discontinue all other treatment and to try cortisone acetate, of which he was given 200 mg. twice on that day. On that evening, some hours after the second dose of cortisone, there seemed to be an improvement in the patient's condition, and during that day 960.5 ml. of urine was obtained by catheter. The subsequent course can be seen in Table I.

On January 1, 1951, the urine showed only +1 albumin, no casts, and only a rare erythrocyte. From January 2 the clinical condition improved every day and catheterization was no longer necessary. From January 5 diuresis, accompanied by intense thirst, was for some days considerable. On January 4 the urea clearance figure was 45. On January 8 the urine showed only a trace of albumin, a few squamous cells, a very rare leucocyte, but no erythrocytes, and no casts.

The patient was discharged from hospital on January 18 apparently perfectly well so far as the kidneys were concerned, with no albumin, casts, or erythrocytes in the urine, no oedema, and still retaining the 80% improvement in his rheumatoid arthritis. During his second stay in hospital it was noticed that an abundance of long silvery hairs had grown on the former areas of alopecia (the normal hair was black). By June the silvery hair had returned to normal colour.

TABLE I.—*Case 1*

Date 1950–1	Cortisone Dosage mg./24 Hours	Urine; ml./24 Hours	Fluid Intake; ml./24 Hours	Average Respiratory Rate per min.	Oedema	Blood Urea mg./100 ml.	E.S.R. mm.	Plasma CO_2-combining Power; Vol. %	Serum Sodium mg./100 ml.	Serum Potassium mg./100 ml.	Plasma Chlorides mg./100 ml.	Eosinophil Count per c.mm.
26/12	—	0	?	38	Tr.							
27/12	—	0	?	40	1							
28/12	—	15 (*c*)	?	52	2	210	72	29·4			480	
29/12	—	210 (*c*)	210	50	3				296	23		200
30/12	—	360 (*c*)	960	40	3	240		18·0				
31/12	400	960·5*(*c*)	1,110·5	44	4							
1/1	400	2,259 (*c*)	1,560	38	4	180		38				50
2/1	300	3,150	2,040	36	4							
3/1	350	3,930	2,660	33	4	264		40	293	17·6		
4/1	300	5,070	2,340	29	4	207						
5/1	250	4,170	2,730	24	4							
6/1	200	4,640	2,400	24	3							
7/1	200	3,810	2,640	24	3							
8/1	150	4,050	2,110	22	2	63	25	40				425
9/1	150	3,360	2,560	21	2				304	13·3		
17/1	50	?	?	18	0	36						
18/1	25	1,500	2,580		0							

(*c*) By catheter. * After 400 mg. cortisone. Under the heading Oedema, Tr. means trace, 1 slight, 2 considerable, 3 marked, and 4 massive. Readmission, 26/12/50. Discharge, 18/1/51.

Case 2

This patient, a married woman aged 36, was studied in co-operation with Dr. Arthur Barry and Dr. M. B. Quane. She was admitted to hospital on June 1, 1951, complaining of almost complete anuria during the previous two days, and severe diarrhoea with some vomiting for three days. There was nothing of importance in her history except the occurrence of sore throats about twice a year between the ages of 15 and 23 years, when they ceased following extraction of 20 teeth. She had a recent recurrence of sore throat, having had two attacks during the month prior to admission. She had had two full-time normal pregnancies preceded by two complete abortions, but with none of these was there a history of toxaemia or of vascular hypertension. Her last menstruation was in November, 1950.

On examination the patient was found to be 27 weeks pregnant. Her pulse rate was 90, respirations 22, axillary temperature 98° F. (36.7° C.), and blood pressure 140/76 mm. Hg. There was slight oedema with pitting on pressure in the lumbar region and in both legs, but no oedema of the eyelids. The tonsils were apparently normal. The pupils reacted to light, and retinoscopy revealed nothing abnormal. The heart was normal, and the baby was alive. She was fully conscious.

On June 2 she complained of headache and "spots" before her eyes. We obtained 199 ml. of urine (partly by catheter) which showed some albumin, a considerable number of leucocytes and erythrocytes, but no casts. Next day the headache continued and the oedema had increased. There was no vomiting or diarrhoea. Bull's diet was started. On June 4 her condition was unchanged, except that she vomited three times. The blood urea was 159 mg. per 100 ml. A throat swab yielded non-haemolytic streptococci. On June 6 the headache was severe, she vomited six times, complained of dimness of vision, and was rather drowsy; 57 ml. of urine was obtained by catheter, and it contained albumin (+4), numerous erythrocytes, some epithelial cells, but no casts or bacteria.

On June 7, as the vomiting was severe, Bull's diet was replaced by 10% glucose drip intravenously (1 litre per 24 hours). The blood urea was 216 mg. per 100 ml. Next

day the vomiting was less, but she was very drowsy. Mr. Duff (urologist) examined her and did not advise surgical treatment. On June 9 she complained of marked dimness of vision and severe headache, and she was semicomatose; she went into premature labour, which resulted in delivery of a living infant weighing 2 lb. 12 oz. (1.25 kg.), at 9.35 p.m. The infant died ten and a half hours later from prematurity; a post-mortem examination was not permitted. On June 9 14 ml. of urine was obtained by catheter. On the same day treatment with cortisone was started (see Table II for details).

On June 10 her condition was unchanged, and, because she was vomiting less, Bull's diet was started again; Hb was 65%. On June 13 her condition was still unchanged. Because of moderate vomiting Bull's diet was discontinued, and an intravenous glucose drip given (1 litre per 24 hours). On June 14 she did not vomit, and there was a slight improvement in her general condition. Some diarrhoea appeared; urine (catheter) contained +2 albumin, numerous erythrocytes, and some granular casts. On June 17 the improvement was continued. There was no vomiting or diarrhoea, and she was able to take fluids orally. Urine contained +1 albumin, fairly numerous erythrocytes, but no casts. On June 18 her general condition was much improved but headaches and dimness of vision were still present; Hb was 44%, and erythrocytes 2,300,000 per c.mm.; oral iron therapy was started. During her stay in hospital her blood pressure varied from 140/110 to 96/56. She was discharged on July 20 apparently quite well.

When seen in October, 1951, she felt and appeared perfectly healthy, and her general physical examination as well as blood pressure, blood count, urine analysis, intravenous pyelogram, and blood urea were normal.

TABLE II.—*Case 2*

Date 1951	Cortisone Dosage mg./24 Hours	Urine; ml./24 Hours	Fluid Intake ml./24 Hours	Average Respiratory Rate per min.	Oedema	Blood Urea mg./100 ml.	Plasma CO_2-combining power; vol.%	Serum Sodium mg./100 ml.	Serum Potassium mg./100 ml.	Plasma Chlorides mg./100 ml.	Eosinophil Count per c.mm.
1/6	0	57	568	22	1						
2/6	0	199	1,136	32	1						
3/6	0	71	1,136	26	2						
4/6	0	28	1,136	36	2	159					
5/6	0	43	1,136	26	2						
6/6	0	57	1,136	26	2						
7/6	0	71	1,136	22	2	216					
8/6	0	57	1,136	22	2						
9/6	200	14	1,136	26	2		30			658	32
10/6	200	114	1,136	24	2	318					
11/6	300	185	1,136	20	2	288					272
12/6	350	213	1,136	28	2	294		309	21		270
13/6	400	327	1,136	22	2	300					123
14/6	400	345	1,136	20	2	320	33			597	73
15/6	400	373	1,278	28	2						
16/6	400	681	1,846	26	2	300	35			620	
17/6	400	1,292	1,420	22	2						
18/6	400	1,452	1,420	20	2	380	41				43
19/6	400	1,481	1,420	22	2					693	
20/6	350	2,130	1,648	20	2	396					25
21/6	350	2,112	1,477	20	2		38				
22/6	300	2,556	1,420	26	2						
23/6	300	2,215	1,448	22	2						
24/6	250	2,187	1,534	18	2						
25/6	250	2,130	1,477	26	2	270					30
26/6	200	2,414	1,562	20	2		57				
27/6	175	2,063	1,477	20	2	186					45
28/6	150	2,613	1,704	24	2						
29/6	100	2,215	1,704	20	2	140					
30/6	75	2,187	1,846	18	2						
1/7	50	2,584	1,420	22	2						
2/7	25	2,783	1,562	24	2	87					120
3/7	25	1,817	1,562	22	2						
4/7	25	2,035	1,704	18	2						
5/7	0	2,035	1,704	20	1						
6/7	0	1,249	1,448	24	1						
7/7	0	1,903	1,364	18	1	72					
12/7	0	1,221	1,221	20	0						
19/7	0	1,876	1,335	22	0						
8/10	0	1,650	2,100		0	30					

Under the heading Oedema, 1 means slight and 2 means moderate.

Case 3

A man aged 45 was referred by Dr. A. F. Falvey to Mr. H. L. Barniville and Mr. J. Corcoran, who after some days of observation and treatment in the Mater Misericordiae Hospital, Dublin, referred him to one of us.

On November 29, 1951, he complained of symptoms of pyrexia. Next day his temperature was 99.5° F. (37.5° C.), his pulse rate regular 80, and there were a few scattered rhonchi at the base of the left lung. At that time there were no urinary symptoms. A dessertspoon of "cremomerazine" was prescribed every four hours with rest in bed and abundant fluids. On December 3 his temperature was normal, but it was discovered that he had taken 4 oz. (114 ml.) of cremomerazine—that is, 16 g. of sulphamerazine—within 48 hours. This drug was then stopped and glucose and an alkaline mixture were prescribed, as on that day he complained of abdominal pain and vomited several times. He was admitted to hospital that afternoon. He passed no urine from admission to hospital on December 3 (except about 30 ml. on December 5) until January 7, when he passed about 18 ml. He was treated by intravenous saline, as frequent vomiting during this period permitted nothing to be retained by mouth.

On December 5 the few millilitres of urine obtained by catheter contained a trace of albumin, a few squamous cells, numerous erythrocytes, but no bacteria, casts, or crystals. Next day a plain *x*-ray film of the abdomen showed no radio-opaque calculi. On December 6 epidural block was performed between L 1 and L 2 with 25 ml. of 1% lignocaine hydrochloride, but no improvement ensued. On the same day a catheter was passed into the left ureter, but a catheter could be passed only for about ¼ in. (1.3 cm.) into the right ureter, apparently owing to blockage; about 18 ml. of urine was collected next day, and the catheter was removed on December 9. On December 7 he vomited frequently. There was a slight mitral systolic murmur; the electrocardiogram showed left axis deviation with a high positive T wave in Lead 4 F. The blood pressure was 174/110 mm. Hg, the pulse rate 80, respiratory rate 28, and the oral temperature 98.4° F. (36.9° C.). He was somewhat drowsy and both eyes had considerable subconjunctival haemorrhages, but the pupils were not contracted. Retinoscopy (by Dr. D. O'Donoghoe) showed nothing abnormal. There was considerable gaseous distension of the abdomen and moderate

oedema of the lumbar region and legs. Some rhonchi were heard at the bases of both lungs.

Treatment with cortisone was started on December 7, and on that day he was given 500 mg. in two doses (see Table III). Next day he was given 400 mg. of cortisone in two doses, and on the same day (29½ hours after the first dose of cortisone) he passed 240 ml. of urine containing +2 albumin, no sugar, no crystals, an occasional leucocyte, and very numerous erythrocytes, but no casts; the nausea had improved so that he was able to drink a moderate amount of fluid. On December 9 he was given 400 mg. of cortisone in two doses, and he passed 4,680 ml. of urine and drank 3,000 ml. of fluid; he had no nausea, vomiting, or oedema, and drowsiness had disappeared. His general condition was improved.

It was decided to reduce drastically the dose of cortisone to see if the diuresis of the previous day was a coincidental phenomenon. On December 10 100 mg. was given twice daily, and on the morning of the 11th 75 mg. No urine was passed from 9 p.m. on December 10 (the day the cortisone dosage was halved) up to 5.30 p.m. on the 11th; 325 mg. of cortisone was therefore given at 5.55 p.m. on December 11 and he passed 390 ml. of urine two hours after this dose (see Table III for details).

On December 19 the urine showed only the faintest trace of albumin and no erythrocytes. The latter never reappeared again up to discharge. On December 24 the urea-clearance figure was 158.

He was discharged from hospital on January 4, 1952, apparently fully recovered. The subconjunctival haemorrhage had by then practically disappeared. He returned to hospital on January 28 and a detailed investigation of kidney function revealed no abnormality.

Case 4

A man aged 64 was studied in co-operation with Dr. B. Mayne in the Meath Hospital, Dublin. He was suffering from symptoms of prostatic enlargement for about one year previous to admission. Prostatectomy was recommended by Mr. Lane, and was carried out by the retropubic method on January 29, 1952.

TABLE III.—*Case 3*

Date 1951–2	Cortisone Dosage mg./24 Hours	Urine; ml./24 Hours	Fluid Intake; ml./24 Hours	Average Respiratory Rate per Min.	Blood Urea mg./100 ml.	E.S.R. mm.	Plasma CO_2-combining Power; Vol. %	Serum Sodium mg./100 ml.	Serum Potassium mg./100 ml.	Plasma Chlorides mg./100 ml.	Plasma Inorganic Phosphorus mg./100 ml.	Eosinophil Count c.mm.
3/12	—	0	?									
4/12	—	0	?									
5/12	—	30±	?		120							
6/12	—	0	?									
7/12	500	18±	?	28	217	46	34·2			442	8·7	25
8/12	400	240	?	24								
9/12	400	4,680	3,000	24								
10/12	200	5,700	3,031	16	246		49·7			494	10·8	50
11/12	400	390*	2,010	16				296	30			
12/12	400	4,080	2,280	18	318		49·7				10	
13/12	400	6,180	4,980	17	184					576	6·8	25
14/12	400	5,880	4,500	18								
15/12	400	4,200	4,020	16				310				
16/12	375	3,330	3,090	16								
17/12	350	3,360	3,990	18	56							
18/12	273	3,450	3,720	17	27							
19/12	250	3,180	2,850	18								
24/12	50	1,350	1,350	22	21							
31/12	0	1,290	1,560	20								
28/1					22	3						25

* No urine passed from 9 p.m., December 10 to 5.30 p.m., December 11 (20½ hours). Patient was given 325 mg. cortisone at 5.30 p.m., December 11, and passed 390 ml. urine two hours afterwards (see text).

TABLE IV.—*Case 4*

Date 1952	Cortisone mg.	Fluid Vol. (oz.) through Catheter	Oral Fluid Intake oz.	I.V. Fluid Intake oz.	Blood Urea mg./100 ml.	Urea, mg./100 ml. in Fluid from Catheter	Plasma-CO_2 combining Power; Vol. %	Serum Sodium mg./100 ml.	Serum Potassium mg./100 ml.	Plasma Chlorides mg./100 ml.	R.b.c. (millions)	Chloride in Gastric Juice
30/1		26	66	40								
31/1		10	110		148							
1/2		5	32		250		45			517		
2/2		1½	40		267		50			529		
3/2		2	32									
4/2		1½	40		365		38			520		
5/2		3	40		435		51	279	22·7	494	2·6	
6/2	400	3½	42		445		51			541		
7/2	500	2½	43		475		62			495	3·2	
8/2	500	2½	38	60	465	455	45			517		
9/2	500	3	28	55	515	545	50	296	24·2	447	3·1	
10/2	500	3½	39									
11/2	500	3½	42		515	502	51	279	28·8	447		
12/2	500	5½	43		635	1,050*	54			446	3·0	329
13/2	500	7	48		690	870	58	298	31·5	423		
14/2	500	5½	50		725	740	62			435		
15/2	500	15	48	20		890						482
16/2	500	19		103	665	910	59	288	30	400	2·6	635
17/2	500	28		99								795
18/2	250	40½		120	650		61	293	31·2	388		846

* Assuming the ammonia present was derived from urea.

Pre-operative examination had not revealed any other abnormality in the urinary system. The blood urea was 37 mg. per 100 ml. The urine was clear and contained no albumin, cells, or casts. An intravenous pyelogram showed normal outline and concentration in both kidneys. Clinical examination revealed a few scattered rhonchi in the lungs and bilateral inguinal herniae. The heart and blood pressure were considered normal. Blood count, chest *x*-ray film, and glucose tolerance were also normal.

Some hours after operation his blood pressure was low, and he was given a transfusion of 2 pints (1,140 ml.) of blood, and 40 oz. (1,140 ml.) of normal glucose intravenously. On the following day he seemed well, but his urinary output was only 26 oz. (738 ml.), and his fluid intake (oral and intravenous) was put up to 106 oz. (3,010 ml.). During the next two days his urinary output continued to decrease (see Table IV). On February 1 an exploratory operation was done on the right kidney and ureter. Oedema of the perirenal tissue was noted, and the capsule over the

lower pole was incised. On February 4 his general condition was good and his mind was clear. Except for sighing respiration there was no other clinical sign to indicate the degree to which uraemia had developed. His blood pressure was 160/75 mm. Hg, and there was no oedema. On that date he was put on a high glucose intake (300 g. daily). Treatment with cortisone was started on February 6. This decision was made reluctantly, as there was no clue to the aetiology of the renal failure. He was given 400 mg., which was increased to 500 mg. the next day.

On February 5 his clinical condition was still good, and his electrocardiogram was normal. At that time his serum potassium was 22.7 mg. per 100 ml. The serum potassium subsequently increased further, and on February 17 the electrocardiogram showed the effect on his myocardium of this rise.

His general condition remained very good until February 15, when it became necessary to aspirate his stomach contents because of vomiting; much bile-stained fluid was withdrawn. At this time fluid was given intravenously and he began to excrete an appreciable quantity of urine again; during the next three days this increased gradually, and for the first time the blood urea ceased to rise; indeed, the blood urea began to decrease, having reached its peak of 725 mg. on February 14. Meanwhile, however, his general condition deteriorated, and he died on February 18 after a short convulsion.

The post-mortem examination report by Professor R. A. Q. O'Meara on the kidneys, suprarenals, heart, and liver, was as follows:

Macroscopically the liver was enlarged, but no gross lesion was seen in it or in the spleen. The kidneys were swollen and pale, and contained a fair number of cortical cysts about ¼ in. (0.6 cm.) in diameter; the pelvis appeared normal. Heart: some hypertrophy of the left ventricle and atheroma of the ascending aorta. Suprarenals much autolysed. Microscopically, the liver showed passive congestion. The kidneys showed: (1) old lesions of chronic glomerulonephritis with hyalinization of glomeruli; (2) recent focal glomerulonephritis; (3) much interstitial oedema; (4) marked congestion of the vasa recta; and (5) some tubules contained pus, others contained blood or altered blood.

Discussion

The onset of anuria in Case 1 appeared to be due to the sudden withdrawal of cortisone, which may have exaggerated an allergic type of reaction in the kidneys following on the throat infection and rash. It was this hypothesis which led us to try the effect of cortisone. The striking improvement in the patient's condition which followed was in agreement with this interpretation. It is debatable whether this patient had an atypical form of acute nephritis, and therefore the possibility that cortisone may be of value in such cases should be considered.

The anuria in Case 2 is difficult to explain and was probably due to mild acute nephritis complicated by pregnancy. Dr. Arthur Barry held the view that it was not entirely a symptom of pregnancy toxaemia for a variety of reasons, including the absence of toxaemia in previous pregnancies and the history of recent sore throats. The response to cortisone was not entirely satisfactory, and it would perhaps be more reasonable to explain, at least partly, the late onset of diuresis by the termination of pregnancy and by the spontaneous recovery which is likely to occur in such cases.

In Case 3 the anuria was interpreted as the result of an acute allergic reaction to sulphamerazine in the kidneys, as there were no sulphonamide crystals in the urine. The diuresis which followed cortisone administration seemed to be attributable to the hormone. This view was substantiated by the recurrence of anuria when the dose of cortisone was suddenly reduced and by the prompt reappearance of diuresis when the dose was increased.

In Case 4 the anuria followed prostatectomy and a moderate degree of glomerulonephritis was found at necropsy. One apparently contributory cause of death was the high blood potassium.

There are theoretical reasons for caution in using cortisone in cases of acute anuria. One may ignore the well-established fact that cortisone acts in animals as an electrolyte-controlling corticoid causing water and salt retention. In humans this effect is less consistent and even contradictory, depending on the condition of the patient. Thus it has an antidiuretic effect in most normal people if the salt intake is above a certain level; it has a diuretic effect in some cases of nephrosis; whilst in toxaemia of pregnancy it may produce internal fluid transfer, causing ascites with diminution of subcutaneous oedema (Moore *et al.*, 1951).

A more serious objection is that cortisone promotes increased tissue catabolism and is therefore apt to increase the concentration of toxic metabolites in the blood. It is thus possible that some of the increase in blood urea noted in the above cases after cortisone administration could be attributed to this effect. A similar explanation may partially account for the increase in serum potassium noted in Case 4.

Another theoretical objection to using cortisone is suggested by its effect on rats' kidneys, resulting in marked hyperaemia of the glomerular capillaries and a shunting of blood towards the medulla, which becomes greatly congested. This may eventually lead to hypertension and nephrosclerosis. Cortisone is also described as aggravating the renal damage caused by mineral-controlling corticoids. Furthermore, cortisone has not a renotrophic effect on the kidney which is characteristic of the anabolic steroids such as testosterone; indeed, it is only the steroids possessing this characteristic which have a protective effect on the kidneys of animals exposed to a wide variety of noxious drugs or violent physical treatment (Selye, 1951). Thomas and Good (1951) reported that cortisone-treated rabbits developed cortical necrosis after intravenous injection of bacterial toxin. Such adverse observations should not be considered decisive for clinical problems, since the reaction of different species is not constant and the doses used are not strictly comparable.

The possibility that an acute allergic reaction in the kidneys to a drug such as the "sulpha" compounds may be controlled by cortisone is of particular interest, as such reactions have often been reported in the literature, especially with sulphathiazole.

Five separate pathological manifestations in the kidney have been attributed to sulphonamide derivatives, and each has been associated with anuria. The best known is mechanical blockage due to crystalluria. The second, that of perifocal tubular nephritis, was recorded by Bergstrand (1946), who also emphasized that the renal findings were essentially the same as those found in the crush syndrome. An acute nephritis resembling the "mercury kidney," with parenchymatous degeneration of the convoluted tubules without inflammatory cell infiltration (More *et al.*, 1946), and a glomerulitis have also been described. Finally, a type mainly distinguished by arterial changes and cellular exudate suggestive of an anaphylactic reaction has been defined by Black-Shaffer (1945). That such reactions may arise after even a small dose of a sulphonamide is exemplified by the case of Bakken (1947).

It is evident from the pathological findings in cases of anuria due to sulphonamides that, while the allergic factor may be inhibited by cortisone, the hope of recovery will depend on whether treatment is given before irreversible changes have occurred in the kidneys. Since the type of allergic reaction is variable it remains to be seen if cortisone will be successful in only a limited number of such cases.

According to our limited experience in the treatment of acute rheumatic fever we believe it is probable that cortisone can not only prevent rheumatic carditis but perhaps even abolish it if given in proper dosage and before irreversible cardiac changes have occurred. If also it be true that cortisone is useful in acute diffuse glomerulonephritis due to allergy, one condition for success would seem to obtain in both these conditions: administration should begin early

in the attack and before organic damage is done to the heart or kidneys. This view was expressed over two years ago by one of us (H. M.) as regards the heart when introducing Professor Philip S. Hench for the Honorary Degree conferred on him by the National University of Ireland.

Summary

Four cases of acute anuria treated with cortisone are reported. In two patients an allergic reaction in the kidneys was suspected, and both responded satisfactorily, making a rapid and complete recovery; in one the allergy was attributed to an overdose of sulphamerazine; in the other it was attributed to the sudden cessation of cortisone, which was being taken (100 mg. daily) for rheumatoid arthritis, and to the development of a sore throat, pyrexia, and rash; both factors preceded the anuria.

No definite conclusions can be drawn from the three apparently successful cases, as acute anuria is prone to develop a spontaneous remission.

We are indebted to Professor W. J. E. Jessop, of the Meath Hospital, Dr. Maurice Hickey, of the Mater Misericordiae Hospital, and Dr. Frank Geoghegan, of the National Maternity Hospital, Dublin, for carrying out the biochemical and pathological investigations. The tables were constructed by Mr. Ronan Kieran, of the Department of Anatomy, University College, Dublin.

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N,N'-DIBENZYLETHYLENEDIAMINE PENICILLIN: A NEW REPOSITORY FORM OF PENICILLIN

BY

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Szabo, Edwards, and Bruce (1951), during a study of the properties of certain penicillin salts, discovered that the coupling of N,N'-dibenzylethylenediamine with penicillin resulted in the formation of a complex only very sparingly soluble in water. These authors described the properties of this complex, its preparation, and the fact that one molecule of base was coupled to two molecules of penicillin. A shortened name for this complex—benzethacil—will be used in this communication. Seifter *et al.* (1951), reporting on the toxicity of benzethacil to animals, found that this compound was approximately 25% more toxic than procaine penicillin to mice by intra-abdominal injection, but was not more toxic when given by intragastric drip, whilst its local analgesic action compared favourably with that of procaine hydrochloride. Elias, Price, and Merrion (1951) followed serum penicillin levels in man after the intramuscular injection of this compound, and concluded that it showed no significant toxicity and gave serum penicillin levels of greater duration than any reported with other forms of repository penicillin.

Benzethacil can be administered orally, and shows therapeutic activity by this route (Lepper *et al.*, 1952), but the present communication deals solely with the serum penicillin levels obtained after intramuscular injection.

Materials and Methods

Penicillin assay was performed by the *Sarcina lutea* plate technique (Food and Drugs Administration, Washington), using *Sarcina lutea* C.P.I.–1001. This technique, which uses penicillin dilutions made up in serum, allows adjustment for the influence of protein-bound penicillin, and is thus of considerable assistance in evaluating the significance of low penicillin levels.

With this technique reproducible zones of inhibition were obtained throughout the period of the experiment, as shown by the figures given in Table I. In practice a complete set of control plates was run with each set of serum assays. Serum penicillin levels were estimated from a line calculated from the individual control plates (see Ungar, 1951).

TABLE I.—*Diameters of Inhibitory Zones of Sarcina Plates*

Standard Penicillin in Serum (units/ml.)	Mean Diameter of Zone of Inhibition in mm.	Standard Deviation
0·10	23·9	±1·2
0·075	20·0	±0·96
0·05	18·8	±1·25
0·03	12·8	±1·45
0·02	9·1	±1·1

Benzethacil was supplied as an aqueous suspension in "tubex" ampoules containing 1 ml. (1 ml. contained 600,000 units of penicillin). The needle provided with the tubex syringe had a diameter of approximately 19 S.W.G.; the suspension could be injected without undue difficulty through this needle.

Nineteen volunteer male subjects took part in this investigation; their ages ranged from 19 to 33 years, and their weights from 10 to 15 st. (63.5 to 95.3 kg.). A single injection of 600,000 units of penicillin contained in one tubex ampoule was given into the gluteal muscles. Blood was withdrawn by venepuncture, and the serum, after being separated by centrifugation, was stored in stoppered bottles over solid CO_2 until used for assay.

Toxicity

Most of the subjects complained of aching at the site of injection for 24 to 48 hours. In no case was this severe. One subject developed a "serum sickness" reaction ten days after the injection. This reaction could not be positively attributed to the benzethacil since another possible antigen had been given shortly before. Despite the lack of positive evidence as to causation, this case is recorded, since benzethacil is excreted extremely slowly, and may give rise to unusual types of sensitivity response.

Results

The serum levels recorded are presented in Table II. It is seen that benzethacil administered by intramuscular injection gives sustained levels of serum penicillin considerably superior to any repository penicillin preparation yet developed. The findings in Table II support the view that even if benzethacil injections were spaced as far apart as 14 days a summation of dose effect might occur.

TABLE II.—*Distribution of Serum Levels following 600,000 Units of Benzethacil Intramuscularly*

Serum Penicillin Levels (Units/ml.)	Time After Injection											
	3 Hrs.	6 Hrs.	24 Hrs.	48 Hrs.	72 Hrs.	5 Days	7 Days	10 Days	14 Days	17 Days	21 Days	24 Days	28 Days
0·10–0·15	4	3	2	1									
0·075–0·099	1	3	2	2	5								
0·05–0·074			2	3	10	1	1						
0·03–0·049					3	2	8	1	1				
0·02–0·029					1		7	7	9	7	6	8	3
<0·02. No detectable level							2	5	6	5	5	2	5
Total observations	5	6	6	6	19	3	18	13	16	12	11	10	8
Range	0·130/ 0·075	0·115/ 0·075	0·115/ 0·070	0·110/ 0·050	0·090/ 0·020	0·050/ 0·035	0.050/ <0·02	0·030/ <0·02	0·040/ <0·02	0·025/ <0·02	0·020/ <0·02	0·025/ <0·02	0·025/ <0·02
Mean	0·104	0·097	0·085	0·076	0·067	0·042							

Though small zones of inhibition were sometimes found at levels of less than 0·02 unit of penicillin, any serum showing less than this level was regarded as showing no detectable amount.

In Table III it is shown that assayable penicillin levels may appear only intermittently in some subjects. This phenomenon is not surprising when the insoluble nature of the preparation and the long duration of action are considered.

TABLE III.—*Cases Showing Intermittent Penicillin Levels*

Subject No.	Days After Injection							
	3	7	10	14	17	21	24	28
1	0·045	0	0	0	0·020	0·020	0·025	0·025
2	0·075	0·030	0	0·040	0·025	0	0·020	0
3	0·080	0·025	0·020	0	0	0·020	0·020	0·020
4	0·050	0·035	0	0·025	0·020	0	0·020	0·020
5	0·020	0·025	0	0·025	0·020	0·020	0·025	0

Discussion

This substance is a most interesting addition to the variety of penicillin preparations now available for therapeutic use. It is as yet too early to do more than suggest what place it may come to occupy in the treatment of disease. Venereal disease, since default from treatment is relatively common, would seem to be a promising field for trial. O'Brien and Smith (1952) have reported on the efficacy of this substance in the treatment of gonorrhoea, while preliminary results in the treatment of syphilis (Roberts, personal communication, 1952) have been said to be highly encouraging.

The prophylaxis of haemolytic streptococcal infection in patients who have suffered from rheumatic fever may be improved by the use of benzethacil. Stollerman and Rusoff (1952), who treated 135 convalescent rheumatic children, concluded that in most cases a single injection of benzethacil will clear the throat of haemolytic streptococci, and that with continued administration at fortnightly intervals there will be no recurrence of the carrier state. Unfortunately, low intermittent penicillin levels provide the optimum conditions for the emergence of drug-resistant organisms, and it is possible that the wide use of benzethacil would increase the magnitude of this problem.

The incidence of sensitization to this preparation is not yet known; but theoretically it may be high, owing to the long-continued exposure of the patient to low and at times intermittent penicillin levels. Preliminary data provided by O'Brien and Smith (1952) and Stollerman and Rusoff (1953) with combined series of 1,500 patients suggest that the incidence of significant penicillin reactions is not greater than 0.3%. In addition, O'Brien and Smith, in a study of four patients who developed urticarial manifestations within ten days of the injection, found that the reaction lasted only two to three days and cleared up whilst assayable penicillin was still present in the blood. However, in view of the unusual nature of the penicillin levels produced by benzethacil further clinical study will be required before the danger of sensitization can be fully assessed.

We are grateful to Wyeth Incorporated, Philadelphia, Pennsylvania, for the supply of "penidural" benzethacil.

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CLINICAL TRIAL OF T.B.3 IN SURGICAL TUBERCULOSIS

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The thiosemicarbazones have been on trial in the treatment of tuberculosis for several years, principally in Germany, and a fair measure of success has been reported.

This report deals with a short clinical trial of one of the drugs, *para*-ethylsulphonylbenzaldehyde thiosemicarbazone (also known as T.B.3, "ethizone," and 8388), in eight patients suffering from tuberculosis of the spine or sacro-iliac joint whose organism was proved, or strongly suspected, to be resistant to streptomycin and P.A.S. We are concerned here mainly with the toxic effects of T.B.3, which in all our eight cases prevented the administration of the drug for long enough to reach any conclusions about its possible bacteriostatic effect on *Mycobacterium tuberculosis*.

Historical Survey

The use of thiosemicarbazones in tuberculosis was first described by Domagk *et al.* (1946). After trying many of these drugs they concluded that the most useful was *para*-acetamidobenzaldehyde thiosemicarbazone (thiacetazone; also known as T.B.1, "conteben," T.B.1/698); their report stimulated extensive clinical trials in Germany.

Donovick and Bernstein (1949) reported that T.B.1 was more active than P.A.S. but less active than streptomycin in early pulmonary infections, but its activity seemed to decline later in the disease. Karlson *et al.* (1949) found that in guinea-pigs T.B.1 and streptomycin, given together, were more effective than either given alone in ordinary therapeutic doses. Hurni (1949), however, working with mice, reported no additive effect of T.B.1 with either streptomycin or P.A.S. separately, though he found that T.B.1 did have some useful effect if given with both streptomycin and P.A.S. together. Heilmeyer (1949) reported good results in exudative lesions and in bone and joint infections. He noted a frequent fall in the erythrocyte sedimentation rate, which, however, did not correspond to any clinical improvement in the disease. He also recorded many toxic reactions, including liver and kidney damage and anaemia.

Hinshaw and McDermott (1950) and Mertens and Bunge (1950) reviewed German results in 10,000 cases. These workers confirmed the activity of T.B.1 against *M. tuberculosis*, but were unable to reach a definite conclusion about the clinical efficacy of the drug, since the trials had been conducted in Germany at a time when the general nutrition of the patients and the facilities for the general treatment of the disease were constantly improving. Toxic symptoms, consisting mainly of digestive disturbances and albuminuria, were fairly common, while profound anaemia developed occasionally after long courses of this treatment. A further possible toxic effect is mentioned by Stadler and Weissbecker (1951), who report a case of transient Cushing's syndrome in a patient receiving T.B.1.

As early as 1949 Hoggarth *et al.*, reporting trials of about 100 thiosemicarbazones and allied substances in infected mice, stated that T.B.3 seemed to be the most effective of these. In 1950 Hoggarth and Martin showed that T.B.3 was superior to P.A.S., though less effective than streptomycin. Martin and Stewart (1950), however, found T.B.3 superior to streptomycin in the early stages of the disease, but this relationship became reversed in more advanced cases. Bavin *et al.* (1950) and Hamre *et al.* (1950) agreed with other workers that T.B.3 was a more effective agent than T.B.1 in experimental mouse tuberculosis.

Rees and Robson (1951) showed that in experimental corneal tuberculosis T.B.3 with streptomycin was more effective than T.B.3 with P.A.S. or streptomycin with P.A.S. Ross *et al.* (1951) recorded encouraging effects from T.B.1 in conjunction with streptomycin and P.A.S. in human renal tuberculosis, but suggested that T.B.3 might be more efficacious and less toxic.

Little seems to be known about the possible toxic effects of T.B.3 in man. Francis *et al.* (1950) showed in monkeys that a dose of 500 mg. per kg. body weight twice daily produced fatty degeneration of the liver, and that 500 mg. per kg. once daily produced no toxic effects. The therapeutic value of this lower dosage in experimental tuberculosis was about half that of 40 mg. of streptomycin per kg. daily. This is equivalent to comparing a dosage in an average man of 3 g. of streptomycin daily with over 30 g. of T.B.3. From the known toxicity of the thiosemicarbazones such high doses in man would clearly be dangerous. Siebenmann and Zubrys (1952) have shown that the haemolytic anaemia produced by T.B.1 in mice does not occur with T.B.3. Spinks (1951) has shown that T.B.3 in mice and dogs produces blood levels four times as high as the same dosage of T.B.1. Since T.B.3 appears to be a more effective substance in the treatment of tuberculosis than T.B.1, it seems reasonable to hope that an effective blood level can be maintained on T.B.3 with less danger of toxic signs than on T.B.1.

Clinical Material

It was decided to conduct a limited clinical trial of T.B.3 in selected cases of bone and joint tuberculosis whose lesions were failing to respond satisfactorily to other forms of treatment. All these patients were appropriately splinted and on a general sanatorium routine in hospital, and all had received appropriate surgical treatment where indicated. All were receiving daily 1 g. of dihydrostreptomycin and 15 g. of P.A.S. Three had developed proved resistance to one or both of these drugs, and in the other five the clinical progress led us to believe that such a resistance must be developing, though we were not able to prove this. In six of the eight patients the lesion was proved to be tuberculous; in one there was histological evidence but no bacteriological proof of tuberculosis; in the eighth the clinical and radiological condition was typical though there was no histological or bacteriological proof of its tuberculous nature.

Dosage.—The first four cases started on 50 mg. of T.B.3 a day and the dose was increased gradually over a period of a few weeks to the maximum of 200 mg. a day in divided doses. The later cases started on 100 mg. a day, and the dose was raised more rapidly to 200 mg. a day. This is the dosage advised by the makers, who warn against exceeding 250 mg. a day.

Routine Investigations.—The following investigations were carried out in all cases: daily urinalysis, weekly haemoglobin estimation, red-cell and white-cell counts, and a fortnightly or monthly erythrocyte sedimentation rate. Blood-sugar estimations and glucose-tolerance curves were done in five cases.

Case Records

Case 1.—A woman aged 30. Tuberculosis of left sacro-iliac joint, onset summer, 1948; not proved. Recurrent sinuses despite streptomycin and P.A.S. Arthrodesis October, 1950. Recurrent wound breakdown. T.B.3 was given with streptomycin and P.A.S. from May 28 to August 7, 1951, when intermittent albuminuria and vomiting led to its discontinuation. E.S.R. rose during the course and haemoglobin fell from 102% to 74%.

Case 2.—A boy aged 9. Tuberculosis of dorsal spine; proved. Treated since 1944. Progressive collapse of thoracic spine and recurrent psoas abscess. Aspirations of psoas abscess; local streptomycin and P.A.S. Organism became resistant. T.B.3 was given from May 31 to August 7, 1951. Intermittent albuminuria and reducing substance in urine. Some anorexia. No anaemia.

Case 3.—A woman aged 64. Tuberculosis of right sacro-iliac joint; proved. Treated by plaster bed, streptomycin and P.A.S., and operative fusion. Organism became resistant, and a course of T.B.3 was added from June 5 to September 21, 1951. Discontinued because of severe albuminuria, profound nausea, vomiting, and anaemia. Haemoglobin fell from 96% to 64%, necessitating blood transfusion. E.S.R. rose. Urine occasionally contained a reducing substance.

Case 4.—A woman aged 31. Tuberculosis of thoraco-lumbar spine; proved. Wound broke down after operative excision of the disease in spite of streptomycin and P.A.S. T.B.3 was given from June 5 to September 27, 1951; discontinued because of albuminuria and severe vomiting. No fall of E.S.R. or haemoglobin. A reducing substance was found in the urine.

Case 5.—A man aged 20. Tuberculosis of D.12 and L.1 and os calcis; proved. Wound broke down following excision of spinal lesion while on streptomycin and P.A.S. T.B.3 was given from June 26 to July 13, 1951, when heavy albuminuria led to its withdrawal.

Case 6.—A girl aged 16. Pott's paraplegia; proved. Failed to improve after plaster-bed and lateral rachotomy. T.B.3 added to streptomycin and P.A.S. from August 24 to September 17, 1951, when severe albuminuria and vomiting led to its discontinuation. E.S.R. and haemoglobin percentage unchanged. A reducing substance appeared in the urine.

Case 7.—A woman aged 69. Dorso-lumbar tuberculosis; proved. Lumbar abscess. Organism became resistant to

streptomycin and P.A.S. T.B.3 was given from September 6 to 25, 1951, when severe nausea and vomiting led to its discontinuation. Mild albuminuria. E.S.R. and haemoglobin unchanged. Reducing substance present in urine.

Case 8.—A woman aged 21. Tuberculosis of lumbar spine; proved. Wound broke down following excision of the disease. Course of T.B.3 was given from September 10 to 27, 1951, when albuminuria led to its discontinuation. Moderate nausea and anorexia throughout the course. E.S.R. and haemoglobin unchanged. Reducing substance was found in urine.

Discussion

No attempt has been made to assess the effect of T.B.3 on the tuberculous lesions in these cases. Since only eight patients were given the drug, and some for only a few weeks, any such deductions would be statistically invalid. We confine our remarks to the toxic effects of T.B.3.

None of this series remained free from toxic signs or symptoms while receiving the drug, and in all of them the drug was withdrawn because of this toxicity.

Albuminuria was found in every case at some time during the course, though its severity varied from case to case. Case 4 developed albuminuria while receiving only 50 mg. of T.B.3 a day, and this did not increase when the dose was raised to 200 mg. a day. In Case 5, on the other hand, very severe albuminuria occurred only when this full dose was reached, the course being immediately abandoned. We found no evidence of permanent renal damage following the courses of T.B.3, and albuminuria disappeared a few days after the drug was withdrawn in all cases. We feel, however, that the persistent albumin leak through the kidneys is evidence that the drug has a very definite toxic effect on this organ, and that long courses of the drug might well lead to irreversible changes.

In all but two of our cases a reducing substance appeared in the urine during the course. In Cases 4, 6, 7, and 8 this was a constant finding, while in Cases 2 and 3 it was intermittent. This substance was shown not to be a sugar, and was probably glycuronic acid, which appears in the urine during the detoxication of P.A.S. in the liver. All these cases were receiving P.A.S.

Only one case tolerated T.B.3 without developing anorexia, nausea, or vomiting to some degree. In Cases 1, 3, 4, 6, and 7 these disturbances were severe on a dose greater than 100 mg. a day, and led to a deterioration in the patient's general health. We were unable to reduce the severity of these symptoms by increasing the intake of glucose or by the administration of "avomine" or chlorbutol. We feel that such a disturbance of the general condition of a tuberculous patient can only do harm.

Case 3 showed a gradual fall of the haemoglobin level throughout the course of T.B.3 in spite of the administration of oral iron. The haemoglobin finally reached a level of 63% after nearly three months on the drug. This patient also experienced severe anorexia and vomiting from time to time during the course. No evidence of any haemolytic element could be found, and the anaemia was of the normocytic hypochromic type. After the course of T.B.3 a blood transfusion and the continued administration of iron soon led to cure of the anaemia.

Case 1 developed a similar type of anaemia but of slighter degree. In neither of these two patients was there any local sepsis at the disease site, and the sinus in Case 1 was at all times sterile. It seems probable that the digestive upsets led to deficient absorption of iron from the intestines. No fall of the white-cell count was seen in any of our patients.

The E.S.R. remained substantially unchanged in six cases and rose in two during the administration of T.B.3. We did not encounter the fall reported by other workers. No case developed any allergic manifestations while receiving the drug.

It is possible that our dosage was too high, but it is of interest that Case 2, an undersized boy of 9, tolerated the full dosage of 200 mg. a day for several weeks a great deal better than most of the adult patients. In view of the work of Francis and Spinks, we felt that no useful therapeutic effects could be expected from a lower dosage.

Conclusions

The serious toxic effects of T.B.3 forced us to abandon this clinical trial in its early stages. Obviously we cannot draw any far-reaching conclusions from this limited experience. We feel, however, that the ill effects of the drug on the general condition of the patients are a very serious contraindication to its use in bone and joint tuberculosis.

The modern combination of a sanatorium regime with the administration of streptomycin and P.A.S. and a planned surgical attack on the disease is in our experience yielding good results. It is important also not to overemphasize the role of chemotherapy in a disease whose basic pathology is the avascular tubercle and caseation, for even the most active antituberculous drug may not reach the living organisms in the centre of the lesion.

The routine use of any fresh chemotherapeutic aids can be justified only if their therapeutic benefits outweigh any toxic effects. The general condition of the patient must not suffer during treatment, and there must be no permanent sequelae.

We believe that T.B.3 fails on the first of these conditions, and that its prolonged administration may lead to failure on the second also. In our opinion its use in bone and joint tuberculosis should be restricted to cases in which other methods are failing to arrest the disease, and in which the situation is becoming so critical that the risks must be accepted.

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At a meeting in Edinburgh on January 7 Dr. Charles Hill, Parliamentary Secretary to the Ministry of Food, discussed the possibilities of derationing some foods (*Scotsman*, January 8). Speaking of the shortage of butter, he said that it was not sufficiently realized that it took 20 pints of milk to make 1 lb. of butter, or that 60% more liquid milk was being consumed to-day than before the war. The drive for more meat had also affected production of butter, but it was hoped that Australia would be able considerably to increase supplies of butter to this country, though it would be unduly optimistic to expect a return to the large quantities of cheap butter which were available before the war. Dr. Hill said that there was enough oil and fat in the world to dispense with the rationing of margarine and cooking fat, but our difficulty was to be able to afford to buy the necessary supplies.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN

A FOUR-YEAR FOLLOW-UP

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In 1950 we reported on the various methods of treatment with streptomycin and the results obtained after at least one year in 33 proved cases of tuberculous meningitis in the Royal Hospital for Sick Children, Glasgow (Russell and MacArthur, 1950). Because it has been recognized that certain children with tuberculous meningitis who have been treated with streptomycin and have apparently made a satisfactory recovery may subsequently suffer a relapse of the disease and die, it was thought necessary to watch the progress of these children for some years after the completion of treatment before claiming that they were cured. The present report is a further record of the 15 children who were alive at the time of the first report. The period of follow-up now ranges from 49 to 68 months. Each survivor was examined during the past year and the cerebrospinal fluid of all but one was examined. Details of these children are recorded in Table I and the case numbers correspond with those in our first report.

The main clinical features of the disease in each of the 33 original cases have already been recorded (Russell and MacArthur, 1950). These were the first patients to be treated with streptomycin in this hospital, but they were not consecutive admissions, because the accommodation available and the time required for the detailed investigations necessary ruled out the possibility of treating all cases admitted for diagnosis and found to have tuberculous meningitis. It was the practice to reserve four cots in each of the two medical units for this therapeutic trial, and when one of these cots was vacated the place was taken by the next case diagnosed. No attempt was made to select cases in which a favourable outcome might be anticipated. The results of treatment are not the best that could be obtained, because the trial was in force at a time when little was known regarding the best method of using streptomycin, and indeed at one stage a number of patients were given only intramuscular injections.

Of the 33 patients, 12 are alive—nine are leading normal lives in their own homes and three are grossly disabled. The cerebrospinal fluid (C.S.F.) is cytologically and chemically normal in 11 of the children. One of the disabled cases (No. 25) has a low sugar content. Table II shows the results obtained in this series and in other published series.

Nine Survivors who are Well

Five of these children were under 4 years old when they developed meningitis. In only one survivor (Case 24) was there a snowstorm appearance on *x*-ray examination, and in one other (Case 32) there was a single choroidal tubercle, now healed. In three children the disease was in its early stages when treatment was begun, and in the other six it was in an intermediate stage. No child has survived in whom the disease was already advanced at the onset of treatment. Two children have had a relapse of meningitis and have recovered after a second course of treatment. A block in the circulation of C.S.F. from the ventricles throughout the subarachnoid space was present in Cases 14 and 22. In Case 14 the block resolved during the period of observation, while in Case 22 a partial spinal block was still present at the time of writing, although he was very well 55 months after the onset of the disease and 52 months after the block was first detected. The parents of the child with the single healed choroidal tubercle (Case 32) refused to bring him to hospital for review, but he was seen in his own home. It was impossible, however, to examine the spinal fluid or to have a skiagram taken. He appeared to be a healthy, happy boy with no abnormal signs in the central nervous system. During August and September, 1951, the C.S.F. of the other eight children was examined and cultured, and was found to be cytologically and chemically normal and sterile.

While the children were under review special attention was paid to their scholastic attainment, but unfortunately it was not possible to have intelligence tests carried out. One child (Case 14), who is of an affectionate and happy disposition, is definitely backward mentally and attends a special school, while Case 11 is probably of low average intelligence. The remaining seven, however, appear to be making good progress at school and do not exhibit any behaviour problems. Recent skiagrams of the skull show areas of calcification in six of these children.

Three Survivors Disabled

One of these children (Case 2) developed meningitis 68 months ago. Though in an early stage of the disease when treatment was begun, she did not respond satisfactorily, and

TABLE I

Case No.	Age (Years)	Stage of Disease at Start of Treatment	Duration of Observation (Months)	Snowstorm Skiagram	Choroidal Tubercles	Spinal Block (B)	Relapse (R)	C.S.F. at End of Treatment				C.S.F. Most Recent				Result	Intracranial Calcification
								Cells per c.mm.	Protein mg. per 100 ml.	Chloride (as NaCl) mg. per 100 ml.	Sugar mg. per 100 ml.	Cells per c.mm.	Protein mg. per 100 ml.	Chloride (as NaCl) mg. per 100 ml.	Sugar mg. per 100 ml.		
2	4	E	68					30	66	761	—	0	36	723	59	Disabled	+
8	3	I	66					90	43	710	—	4	36	725	59	Well	+
9	6	I	47				R	350	281	699	30	—	—	—	—	Dead	+
10	2	E	60				R	5	38	765	53	—	—	—	—	,,	+
11	5	I	63					12	65	770	—	1	24	743	61	Well	+
12	2	I	63				R	55	73	729	—	1	19	762	48	,,	+
14	11	I	58			B		70	277	658	—	0	42	748	73	,,	+
15	3	I	58				R	40	31	756	—	2	27	734	48	Disabled	+
22	4	E	55			B		1	41	713	—	0	38	—	61	Well	
24	6	E	53	+				26	41	629	77	3	40	764	61	,,	
25	1	I	52				R	35	82	681	—	4	27	735	37	Disabled	
28	3	E	51					17	37	717	50	2	34	758	63	Well	+
29	2	I	51					49	50	716	56	1	30	682	53	,,	+
32	3	I	49		+			10	72	676	—	Refused permission				,,	?
33	7	E	42	+	+	B	R	4	4	625	32	—	—	—	—	Dead	

E=Early stage. I=Intermediate stage.

TABLE II.—*Recorded Results in Tuberculous Meningitis Treated with Streptomycin*

Author	Minimum Observation Period (Months)	No. of Cases			
		Total	Alive	Well	Disabled
Illingworth and Lorber (1951)	12	82	36 (44%)	24 (29%)	12 (15%)
Lincoln and Kirmse (1949) (promizole also given)	12	10	8 (80%)	5 (50%)	3 (30%)
Cairns *et al.* (1950)	12	60	30 (50%)	21 (35%)	9 (15%)
Cathie and MacFarlane (1950)	12	60	28 (47%)	23 (39%)	5 (8%)
McCarthy and Mann (1950)*	16	37	14 (38%)	12 (32%)	2 (6%)
Russell and MacArthur (1950)	12	33	15 (45%)	10 (30%)	5 (15%)
Present series	49	33	12 (36%)	9 (27%)	3 (9%)

* In this series six children treated with intramuscular streptomycin alone have been excluded from the figures quoted.

tubercle bacilli were still cultured from her C.S.F. two and a half months after the start of streptomycin therapy. After six months of intramuscular and intrathecal treatment her clinical condition was deteriorating and she developed convulsions and a right-sided hemiplegia. Treatment was finally stopped after 12 months, when she was hemiplegic and having convulsions. The disease is now quiescent and her C.S.F. is normal and sterile on culture, but the child is a low-grade mental defective with a right-sided hemiplegia and has frequent epileptic fits. Calcification is apparent in a recent skiagram of her skull, and is situated above and anterior to the sella and on both sides of the midline.

Case 15 has been observed for 58 months. He had intramuscular treatment alone for 60 days, after which tubercle bacilli were still cultured from his C.S.F. and he was emaciated and comatose. Ten weeks of combined intramuscular and intrathecal treatment brought improvement in the cerebrospinal-fluid findings, but his clinical disability remained severe. He suffered a relapse of meningitis 15 months after his initial attack and had a further three months of intramuscular and intrathecal treatment. The disease is at present quiescent and the C.S.F. is normal, but he is mentally defective with a right hemiplegia, has epileptic fits, and shows marked sexual precocity. Intracranial calcification began to appear 23 months from the onset of the illness, and there is now a dense mass above the sella turcica and on the left side of the brain.

Case 25 has now been under observation for 52 months. He was 12 months old and was in an intermediate stage of the disease when the diagnosis was made. He had a three-months course of intramuscular and intrathecal treatment, on the completion of which he was blind, he was having convulsions, and his C.S.F. was still abnormal. Six months later, however, his spinal fluid was normal, although he was mentally defective and was still having convulsions. Two years after his initial illness he had a relapse of meningitis, and again tubercle bacilli were cultured from his C.S.F. He was given another three-months course of intramuscular and intrathecal streptomycin with some improvement. At the present time he is mentally defective, has epileptic fits, and his C.S.F. sugar is at an ominously low level.

Changes Since last Report

Comparison of the present state of this series with the state in September, 1949, shows four changes, one for the better and three for the worse. Case 32 was reported as disabled because he was believed to be developing hydrocephalus, but he has completely recovered and attends school regularly, where his achievements are well up to the average standard. One inactive choroidal tubercle is still visible in his right eye.

Case 33, who was disabled at the time of the last report, has since died, 30 months after the onset of the disease. This boy was admitted to the centre with miliary tuberculosis and developed meningitis while on intramuscular treatment. Until his death 30 months later he was under continuous observation and had four relapses, at the onset of three of which tubercle bacilli were cultured from his C.S.F. In the final episode the tubercle bacilli were still sensitive to streptomycin, but he died suddenly on the day after the start of treatment. At necropsy the brain showed hydrocephalus, with a thick gelatinous exudate at the base of the brain, and four small tuberculomata were found in the cortex.

Case 9 was classified as "well" in the original report, although nine months after the completion of treatment his C.S.F. still had a raised cell count. He remained at home, leading a normal life and attaining average success at school, but 45 months after his initial meningitis he had a relapse and in spite of treatment died within two months. This boy showed the most scattered intracranial calcification of the series, the nodules being widely spread on both sides of the brain. The course of the illness during the first six months was stormy, with episodes of convulsions, aphasia, hallucinations, facial palsy, and severe psychological upsets. Three months after stopping streptomycin it was realized that he was deaf, but gradually his deafness diminished, and a year later his hearing, by rough tests, was normal. It seems probable that his deafness was due to the disease rather than to the streptomycin sulphate with which he was treated.

Case 10 was classed as "well" in our 1949 report, but in October, 1949, he was found to have a tuberculous abscess in the anterior end of the left seventh rib. This discharged pus containing tubercle bacilli, and the child was given a four-weeks course of intramuscular streptomycin. The lesion healed completely and permanently within three months. An *x*-ray film of the skull in February, 1951, showed extensive intracranial calcification at the base of the brain. During 1951 the boy remained apparently well, though there was a mild right-sided hemiplegia, and he attended school regularly. On August 22 a lumbar puncture was done during routine follow-up studies. The C.S.F. was cytologically and chemically normal and he seemed very well, but it was disquieting to culture two colonies of tubercle bacilli from the C.S.F. In May, 1952, he had a relapse of tuberculous meningitis and in spite of intramuscular, intrathecal, and intraventricular treatment he died with gross hydrocephalus eight weeks later. In this relapse, three years after his primary attack, the tubercle bacilli were fully sensitive to streptomycin.

Intracranial Calcification

One of the most interesting features of the follow-up has been the detection of intracranial calcification. This has been present in the skiagrams of 8 of the 12 survivors and also of two children (Cases 9 and 10) who died of a relapse of meningitis in March, 1951, and June, 1952. In every case there have been calcified areas in the vicinity of the sella turcica. In five children central nodules were seen around the sella or just above it. In six cases there were nodules a little above the level of the sella and about one-third of the distance towards the left side of the skull, and in two cases the nodules were on both sides of the film. The majority of calcified foci appeared to be in the vicinity of the cisterna interpeduncularis and cisterna chiasmatica, and in one case the calcification extended up towards the cisterna ambiens. This localization was supported by the findings at necropsy on Cases 9 and 10, whose skiagrams showed widespread intracranial calcification. There were numerous calcified foci in the tuberculous exudate at the base of the brain, often deep in the sulci, but no calcified areas in the brain substance.

Cairns (1951) stated that "in tuberculous meningitis it is probably many months before the subarachnoid spaces are clear of exudate; in some successful cases traces of it persist indefinitely and become calcified." From the present findings it would seem that in the successful cases calcification is the rule rather than the exception, and it is probable that its appearance depends mainly upon the length of time

since active meningitis occurred. The earliest appearance of calcification in the basal cisterns was noted at 23 months from the onset of meningitis. In two of the children the areas concerned may well be within the brain parenchyma. Case 15, who shows signs of precocious puberty, has a dense mass, probably situated in the hypothalamus. Case 14, before the onset of meningitis, was admitted to a neurosurgical unit for investigation of a cerebral tumour. At that time, in November, 1947, a skiagram of the skull showed an area of calcification in the left temporal lobe. Ventriculography revealed that there was also a large mass in the right frontal area blocking the anterior horn of the right lateral ventricle. A second area of calcification has been present on films dating from 15 months after the onset of meningitis, and the site appears to correspond with the tuberculoma found in the right lateral ventricle. It is not surprising to find that seven of the ten children showing intracranial calcification also show intrathoracic calcification.

Other published accounts of tuberculous meningitis treated with streptomycin have been searched for any reference to the presence of intracranial calcification in surviving patients. Lorber (1951) described intracranial calcification in a girl of 7 years who developed tuberculous meningitis 18 months previously. This girl showed signs of sexual precocity, and in her case there were two small foci of calcification believed to be in the wall of the third ventricle. The demonstration of intracranial calcification which is now possible in so many of these cases is a vindication of the view (Rich and McCordock, 1929) that meningitis is commonly secondary to cortical or meningeal tuberculomata.

Relapse of Meningitis

In this series there have been nine children who suffered recurrence of meningitis at intervals of 3 to 179 weeks after the completion of treatment (Table III). Six children have

TABLE III.—*Relapses of Tuberculous Meningitis*

Case No.	Interval Since Last Treatment (Weeks)	Last C.S.F. Taken Before Relapse: Interval Before Relapse (Weeks)	Cells per c.mm.	Protein mg. per 100 ml.	Chloride (as NaCl) mg. per 100 ml.	Sugar mg. per 100 ml.	Present Condition
3	36	9	40	76	719	38	Dead
5	3	3	20	57	764	—	,,
9	179	128	31	26	727	—	,,
10	(1) 4	2	130	59	695	25	
	(2) 179	27	1*	31	693	83	,,
12	80	57	12	24	702	—	Well
15	36	6	9	58	650	51	Disabled
25	88	16	4	30	693	71	,,
26	5	3	13	90	674	20	Dead
33	(1) 5	5	42	83	686	18	
	(2) 4	2 V.P.	15	7	667	45	
	(3) 49	12 spinal	1	—	660	58	
	(4) 32	4 block persists	2	32	604	69	,,

* Tubercle bacilli cultured. V.P.=Ventricular puncture.

died. Only in Case 25 had the C.S.F. been normal before the relapse occurred, but physically he was severely disabled. In Case 10 the C.S.F. was cytologically and chemically normal but tubercle bacilli grew on culture. One relapse which occurred after three and a half years of good health was particularly disappointing. This child (Case 9), in an intermediate stage of the disease when treatment was begun, had intramuscular and intrathecal treatment during a period of three months. Reference has already been made to the severity of the clinical picture. Ten months after the completion of treatment his C.S.F. was still abnormal, although his only physical disability was some impairment of hearing. He remained at home, and was doing well at school until January, 1951, when he had a relapse of meningitis with tubercle bacilli in the C.S.F. In spite of treatment he died six weeks later. A skiagram taken on January 30 showed extensive intracranial calcification, and at necropsy numerous calcified tubercles were found in a dense basal exudate but none were present in the brain substance. The appearance of intracranial calcification is therefore not an infallible sign of healing of the meningitis; it does not preclude the existence of tuberculous foci which may still contain living tubercle bacilli. Cases 9 and 10 had extensive intracranial calcification when they developed a recurrence of meningitis and died.

Cortical or subcortical tuberculomata have been detected after death in only two of the six children who died after a relapse, and in only 7 of the 20 necropsies performed in the whole series. Hydrocephalus of marked degree was found in five of the six fatal cases of relapse, and the thickness of the basal exudate aroused comment in three. Tubercle bacilli were cultured from the C.S.F. withdrawn at the onset of the relapse in six of the nine children. Unfortunately, it was possible to test the streptomycin sensitivity of only two of these cultures (Cases 10 and 33). The bacilli were as sensitive to streptomycin as at the beginning of treatment more than three years previously, although there had been adequate opportunity for resistance to develop.

Type of Streptomycin and Neurotoxicity

All the children in this series were treated with salts of streptomycin—hydrochloride, sulphate, or calcium chloride complex. During their relapse three children were given dihydrostreptomycin for short periods, but no untoward effects were noted. On the basis of this limited experience of the comparative action of the two drugs we are unable to assess the relative toxicity of streptomycin and dihydrostreptomycin in the present series of cases.

Summary

Thirty-three patients with tuberculous meningitis have been treated with streptomycin and the survivors have been re-examined from four to five and a half years after the institution of treatment.

Nine (27%) are alive and well and leading normal lives, three are gravely disabled, and 21 have died after periods ranging from 2 days to 60 months.

Spinal block occurred in nine of the patients—seven are dead, and a partial block persists in one of the two survivors.

Intracranial calcification as seen in skiagrams has occurred in 10 of the 13 patients who survived long enough for it to develop. Six of these are well, two are disabled, and two have since died.

Relapse of meningitis has occurred in nine cases. Only one of these children is alive and well, two others are disabled, and six have died of the relapse.

We wish to thank the late Professor G. B. Fleming, Professor Stanley Graham, and Dr. James H. Hutchison for access to the case records and for advice in the preparation of this paper; and the staff of the biochemistry, pathology, and radiology departments for their arduous investigations.

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The first report of the W.H.O. Expert Committee on Public Health Administration is now available as No. 55 in the *World Health Organization: Technical Report Series*. In the committee's opinion, the main functions of the central authority should be the formulation of policy, the giving of advice and specialized technical assistance to local authorities, and the enforcement of medical legislation and other standards of efficiency; while the main function of the local health administration should be operational.

USE OF SUCCINYLCHOLINE IN E.C.T.

WITH PARTICULAR REFERENCE TO ITS EFFECT ON BLOOD PRESSURE

BY

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In recent years it has been possible to apply electric convulsion therapy to a wider range of cases than previously, with the aid of curare-like substances to weaken the muscular spasms of the convulsion. For the specific requirements of E.C.T. the newly introduced short-acting group of muscle relaxants is particularly appropriate. This paper deals with the practical problems that arise during this type of treatment and the methods of dealing with them. Certain theoretical problems are also discussed.

The contraindications to convulsion therapy, in otherwise suitable patients, are usually classified into two groups : those due to the effects of the convulsion itself —for example, damage to bones, damage to tuberculous lesions in the lung—and those due to the strain on the cardiovascular system, particularly incipient heart failure and hypertension. Since depression, for which E.C.T. is usually given, becomes more common with increasing age, hypertension becomes the most frequent contraindication to treatment. There has been much discussion on this problem. Kraemer (1950) measured the blood pressure immediately before the shock, and 2, 5, 10, 30, and 50 minutes afterwards. The average rise of pressure was 40/10 mm. Within 10 minutes it had returned to normal. He concluded that moderate hypertension was not a contraindication to E.C.T. In some preliminary measurements we found that the B.P. is extremely variable, undergoing a number of phasic changes during different stages of the convulsion and immediately afterwards.

Eyman and Morris (1950) discussed fatalities associated with E.C.T., and emphasized the risks of cardiac abnormality. They recommend that an E.C.G. should be taken before treatment is given wherever cardiac involvement is known or suspected. On the other hand, Piette (1950), who agrees that most of the fatalities are due to cardiac failure, thought that in such cases there may often be no clinical or E.C.G. abnormality in the cardiovascular apparatus. This is in agreement with Bankhead, Torrens, and Harris (1950), who state that cardiac reactions are due to overactivity of the vagus, and are of the opinion that they can be eliminated by premedication with atropine. There is no doubt that E.C.T. produces a rise in blood pressure, although this is of fairly short duration. In practice very few fatalities have occurred, but the possibility cannot be excluded that this is partly because of the caution exercised by physicians in the selection of cases for treatment.

The use of relaxants in E.C.T. has been recommended on the grounds that it reduces the strain on the heart produced by the convulsion, so that the presence of hypertension can be regarded as an indication for their use. It was therefore decided to investigate the changes in blood pressure which occur in E.C.T. when relaxants are used. So far as we are aware, this has not previously been studied ; the paper by Davies and Spencer Paterson (1952) dealt with the hypertensive effect of electronarcosis. Piette (1950) stated that curare does not suppress the rise in blood pressure due to E.C.T., but if it is used with sodium thiopentone, atropine, and oxygen the variations in arterial pressure which normally appear are entirely avoided. Since the shorter-acting relaxants can be used not only to " soften " the convulsion but to eliminate it completely, without at the same time producing respiratory difficulties afterwards, it would seem that they are eminently suitable for this purpose. This investigation is therefore confined to the use of succinylcholine (" scoline ").

No attempt was made to select patients, who came from our own wards. They were all women, chiefly elderly, feeble, and hypertensive, with a few younger healthy ones.

Methods

The procedure was as follows. Blood pressures were taken with an aneroid-type sphygmomanometer, because it is speedy and convenient in use. They were taken immediately before the injection of sodium thiopentone, one minute after that injection, again after the injection of succinylcholine had become effective, and, lastly, immediately after the convulsion was over. The moment selected for taking the B.P. after the injection of succinylcholine was when the fibrillation produced by the drug had ceased, and therefore when paralysis was complete. Preliminary trials showed that 0.2 g. of sodium thiopentone was enough to produce unconsciousness in most of our patients, and this amount was always used. It is not often that more would be required, except for very big patients. The recommended dose for succinylcholine is 1.2 ml. of a 5% solution, but we found that 1.5 ml. produced complete relaxation in our patients and did not give rise to any difficulties. More could be given, and we have done so, but, again, the larger dose would in general be required for only very muscular patients. The lungs were inflated two or three times with oxygen containing 5% carbon dioxide, just before a shock of 30 joules was given.

Results

The results of these preliminary trials showed the expected drop of blood pressure after sodium thiopentone medication, but an unexpected rise was almost invariably found after the injection of succinylcholine. This rise was not further increased by the convulsion. The accompanying Table gives the results in 12 consecutive cases. The rise in B.P. demonstrated in the Table is statistically very highly significant. A similar rise after the injection of succinyl-

Blood Pressure in Patients Given E.C.T. After Sodium Thiopentone and Succinylcholine (Recorded to Nearest 5 mm.)

At Beginning	After Thiopentone	After Succinylcholine	After Fit
160/95	130/95	160/110	170/90
150/90	120/80	120/80	140/80*
160/90	145/85	185/120	180/100
160/80	150/75	190/130	160/100
140/80	130/75	150/100	180/100
140/90	110/75	170/105	160/90
140/80	110/70	140/90	150/90
125/90	120/80	140/90	100/60*
175/105	140/90	220/160	200/110
150/100	150/80	195/100	180/100
140/90	130/80	200/150	190/110
160/90	135/80	180/160	200/100

Mean B.P. after sodium thiopentone 130·8/80·4 mm.
Mean B.P. after succinylcholine .. 170·8/116·2 mm.
Difference 40·0/35·8 mm. ±S.D. 22·6/26·5 mm.
Number of cases=12.
t=6·2/4·7. P is <0·001/<0·001.
* Part of the succinylcholine leaked out of the vein in these cases.

choline was found in each of the subsequent experiments. The overall effect of this substance—that is, the change from the initial B.P.—is, of course, not so great, but it is still highly significant statistically.

It is possible that this increase of B.P. might be due to the delayed effects of the sodium thiopentone. A control series was therefore investigated in which succinylcholine was replaced by the same volume of sterile water, and the B.P. taken after the same interval. Subsequently, the normal procedure was completed. It was found that the injection of sterile water had no significant effect on the blood pressure. The results were as follows:

No. of cases	10
Mean B.P. after sodium thiopentone	122.3/75.4 mm.
„ „ „ sterile water	121.8/74.5 mm.
Difference: −0.5/−0.9 mm. ± S.D. 7.8/9.1 mm.	

This proves that the rise must be due to the succinylcholine.

This rise in B.P. produced by succinylcholine is not very great, but if the relaxant is to be used for borderline cases in which any strain on the heart might be dangerous it is a matter of practical importance. It was decided to investigate the possibilities of ganglion-blocking agents in preventing this rise. The two substances tested were tetraethylammonium bromide (T.E.A.B.) and hexamethonium iodide ("hexathide").

Preliminary trials showed that both ganglion-blocking drugs achieved their maximum effects in two minutes, and that the optimum dose of hexamethonium iodide was 2 ml. of a 2% solution. The new procedure was as follows. After the first B.P. reading 2 ml. of hexamethonium iodide was injected, followed immediately, through the same needle, by the normal dose of sodium thiopentone. The B.P. was taken one minute after this, the rest of the procedure being identical with that in the first experiment. The results of this new procedure were satisfactory, and demonstrated that this dose of hexamethonium iodide did not produce a profound fall of B.P. and was enough to prevent the B.P. rising above the normal for the patient even after the convulsion. The results were:

No. of cases	10
Mean B.P. at the beginning	171.0/96.0 mm.
„ „ after fit (preceded by hexamethonium iodide 2 ml., thiopentone, and succinylcholine)	139.0/88.5 mm.
Difference: −32.0/−7.5 ± S.D. 27.3/21.2 mm.	

This procedure was repeated, using T.E.A.B. instead of hexamethonium iodide. It was found that 1 ml. of a 10% solution was just enough for most cases. The results were:

No. of cases	9
Mean B.P. at the beginning	159.4/91.1 mm.
„ „ after fit, etc.	152.8/92.8 mm.
Difference: −6.6/+1.7 ± S.D. 29.4/22.0 mm.	

The results with 2 ml. are but little more effective for the average case:

No. of cases	10
Mean B.P. at the beginning	184.5/93.5 mm.
„ „ after fit, etc.	168.0/92.5 mm.
Difference: −16.5/−1.0 ± S.D. 31.4/11.73 mm.	

Discussion

The most important of our observations is the undoubted rise in B.P. following an adequate relaxant dose of succinylcholine. This has previously not been described in the literature; in fact, succinylcholine in clinical doses has been stated to have no effect on the arterial pressure. Experiments on animals have shown that a dose of 25 times the normal, or even higher, is required to produce any increase in the B.P. The difference between this and the results found in our patients is probably a species difference. Since the hypertensive effect of succinylcholine is not eliminated by blocking the autonomic ganglia, either it must be due to an interference with the action of the blocking agent or it acts peripheral to the ganglion. If it be the former, then succinylcholine must have a reaction similar to the "nicotinic" action of acetylcholine. It is evident that the question can be settled only by experiment, preferably on human tissue. This is outside the field of this paper, which is restricted to purely clinical matters.

Smaller doses of succinylcholine would have much less effect on the B.P., but then the specific value of this drug would be lost. It can be used to produce a paralysis so complete that no muscular activity can be seen at all during the "convulsion." This eliminates all strain on the cardiovascular system from that particular aspect—which is confirmed by the fact that the patient remains quite pink throughout. Furthermore, recovery from a full dose is just as rapid as from a smaller dose, unlike the longer-acting relaxants. Previous reports have indicated that the latter do not increase the B.P. This would be a contraindication to the use of succinylcholine were it not for the fact that the convulsion itself produces such a rise. If a ganglion block be used to deal with this, it can be used also to cover the hypertensive effect of the succinylcholine.

It was noticed on two or three occasions that after the injection of succinylcholine the pulse became irregular, apparently owing to extrasystoles. It is unlikely that such irregularities are common, and, in any case, they were never observed when the autonomic ganglia were blocked.

We have the impression that the effect of blocking the autonomic ganglia is greater in those patients with the higher blood pressures. This is probably true, but would require a special investigation, with careful standardization of many factors, to test it adequately.

Practical Points

The statistics given are based on a limited number of cases dealt with by the technique described. This, however, is unnecessarily elaborate for routine work, and normally all that would be required would be the following:

1. We consider that an injection of atropine should always be given, to reduce salivation and excessive bronchial secretion. When a relaxant is to be used it is important that the patient should be placed in a comfortable position, to prevent strain on the ligaments when not protected by the tone of the muscles.

2. Sodium thiopentone and succinylcholine may be mixed in the one syringe, provided this be done immediately before injection. This enables a one-syringe technique to be used when no ganglion-blocking agent is given.

3. The ganglion-blocking agent should be given before the mixture of thiopentone and succinylcholine, as the former takes slightly longer to produce its full effect.

4. If a few breaths of oxygen be given before the shock the patient stays pink throughout. In our experience with succinylcholine, running into several hundred administrations, we have never observed prolonged apnoea, which, we think, may be due to an unsuitable technique.

5. It has been our practice to press upon the epigastrium just before the current is passed, to prevent the patient waking with a stomach distended by the oxygen used for inflation.

6. *The Convulsion.*—With complete relaxation it is difficult to determine whether an adequate convulsive dose has been given. We have employed two methods for this purpose: (*a*) By noting the autonomic component of the cerebral discharge which constitutes the fit; the simplest observation is to look for dilatation of the pupils, and, particularly, injection of the conjunctivae. (*b*) As this method is not always accurate with ganglion-blocking agents we have devised a specific manœuvre to demonstrate the presence of the fit. Immediately before succinylcholine is injected a tourniquet or a sphygmomanometer cuff is fixed round the opposite arm. If this be kept tight enough to compress the artery until the current is passed the effects of the shock will be observed in that arm only. Thus the patient may be seen lying absolutely motionless apart from a slightly modified clonic fit in the blocked arm. By this means one is never in doubt about the effectiveness of the current.

Summary

Succinylcholine is a safe relaxant for E.C.T.

It can be used to abolish the convulsion completely; even with the doses necessary to do this the patient's recovery from the fit is always rapid.

Succinylcholine produces a slight rise of blood pressure which is generally unimportant. If necessary, this can be controlled by blocking the autonomic ganglia.

When complete muscular relaxation is advisable succinylcholine can be administered with safety without any elaborate system of dosage. In such cases the presence of a fit can be detected by the simple manœuvre described.

We wish to thank Dr. H. C. Beccle, physician-superintendent, for his advice and encouragement, and for permission to publish. We are grateful to our nursing staff for their help and forbearance over the additional labour we have imposed on them. We are indebted to Allen & Hanburys Ltd. for the supply of "hexathide" used in this investigation.

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CANICOLA FEVER

A HUMAN CASE IN NORTHERN IRELAND

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In 1931 Klarenbeek and Schüffner (1933) isolated *Leptospira canicola* from the urine of a dog. This discovery was soon followed by the recognition of *L. canicola* infections in man (Dhont *et al.*, 1934). Baber and Stuart (1946) reported the first human infection in England; Joe and Sangster (1951) published the first cases in Scotland, although Stuart (1938), in a survey of Glasgow tripe-workers, had found agglutinins in low titre to *L. canicola* in the serum of a woman who gave no history of illness. In the four-year period 1947–50 70 cases were diagnosed in England and Wales (Broom, 1951). Figures given by Alston (1951) show that 25 cases occurred in 1949 and 33 in 1950.

Broom (1951), in a review of leptospirosis in England and Wales, drew attention to the fact that no human case of canicola fever had yet been reported from any part of Ireland, although his survey of the incidence of the disease in Dublin dogs had shown the infection rate in that city to be as high as in England.

The case recorded here is, we believe, the first serologically proved human infection with *L. canicola* reported from Ireland.

Case Report

A muscular and well-nourished man aged 36 was admitted to a surgical unit of the Belfast City Hospital on February 1, 1952. Eight days before admission he complained of feverishness and shivering attacks of abrupt onset. He was forced to give up work six days before admission, and he took to bed one day later. He then developed pains in the legs, lumbar regions, and right renal angle; these were severe and disturbed sleep. Other symptoms were colicky pains in the right hypochondrium and epigastrium, loss of appetite, vomiting, tiredness, photophobia, and very severe frontal headache. Frequency of micturition, dysuria, and oliguria caused him to summon his medical attendant, who visited him on January 29 and found his temperature to be 102° F. (38.9° C.) and the urine to contain a heavy cloud of albumin. A tentative diagnosis of acute pyelitis was made and treatment by oral sulphatriad instituted. The pyrexia promptly subsided, but nausea and vomiting became troublesome, and admission to hospital was arranged.

On admission his temperature was 98° F. (36.7° C.), pulse 104, and respirations 22. Clouding of consciousness was considerable; there was no neck rigidity, and Kernig's sign was negative. The face was flushed and the conjunctivae were markedly congested and suffused. Jaundice was absent. A patchy erythema was noted on the chest, also labial herpes. The tongue was coated. Slight tenderness was elicited over the right upper abdomen, the liver and spleen were not palpable, and the renal angles were free. The urine was acid and contained a trace of albumin with scanty red blood cells but no pus or organisms. On the day after admission the temperature rose to 99.2° F. (37.3° C.), but afterwards remained subnormal.

The patient was seen at this stage by one of us (A. C. H.), and the possibility of leptospiral infection was discussed. He was transferred to a medical unit for further investigation, although clinical recovery was rapid and uneventful. Discovery of a positive leptospiral agglutination prompted an exhaustive inquiry into the history of the case, and it was found that the patient's dog had sickened and died after a few days' illness, during which the patient had tended the animal and handled it a great deal. The patient first felt unwell about three days subsequent to the dog's death. He worked as a labourer in a bakery which was infested by rats and required periodical deratting. One such campaign had occurred about a week before the present illness.

The patient insisted on being discharged on February 11, before an effective penicillin course could be completed. Shortly after leaving hospital the muscular pains reappeared and a pustular rash developed on his face. He returned to hospital on his doctor's advice two weeks after his initial discharge. On this occasion his general condition seemed satisfactory, and the limb pains rapidly subsided. He was given a penicillin course (2,000,000 units daily, intramuscularly, for 12 days) and the laboratory tests were repeated. The leptospiral agglutinations of the other members of the household and of three fellow workers were examined.

Agglutination Tests

The technique of the agglutination tests was Broom's (1948) modification of that of Schüffner and Mochtar (1927). The first specimen of blood, taken on the 12th day of illness, agglutinated *L. icterohaemorrhagiae* and *L. canicola*, both to titres of 1 in 300. (In the early stages of leptospirosis equal or nearly equal titres are common.) Subsequent specimens, taken over a period of weeks, gave agglutinations which showed a falling away of the heterologous titre, while the homologous titre remained high (see Table I).

It will be seen that the second specimen of blood serum (taken on the 19th day of illness) gave agglutination in higher titre for *L. canicola*; this serum was sent to Dr. J. C.

TABLE I.—*Leptospiral Agglutination Tests*

Duration of Illness	Reciprocal of Titres	
	L. icterohaemorrhagiae (Strain Jackson)	*L. canicola* (Strain Utrecht)
12th day ..	300	300
19th ,, ..	1,000	300. ± at 1,000. Trace at 3,000
48th ,, ..	300. Trace at 1,000	3,000
66th ,, ..	100	1,000. Trace at 3,000

Broom for confirmation. In view of the nearly equal titres for both *L. icterohaemorrhagiae* and *L. canicola*, a cross-absorption test was carried out. Dr. Broom's result is shown in Table II, clearly demonstrating *L. canicola* as the infecting organism.

In addition, agglutination reactions against *L. icterohaemorrhagiae* and *L. canicola* were performed on blood samples from the patient's wife and eight children, and from three of his workmates. All results were negative.

TABLE II.—*Results of Cross-absorption Test*

	Reciprocal of Titres	
	L. icterohaemorrhagiae	*L. canicola*
Unabsorbed	1,000	1,000. Trace at 3,000
Absorbed:		
L. icterohaemorrhagiae	0	300. Trace at 1,000
L. canicola	0	0

0 = Negative in all dilutions from 1/30 upwards.

Other Laboratory Investigations

The blood urea was 100 mg. per 100 ml. on May 4, 44 mg. on May 7, and 38 mg. on May 26. On May 5 the white blood cells numbered 16,300 per c.mm. On May 27 the cerebrospinal fluid (examined after readmission) was normal, and the erythrocyte sedimentation rate 4 mm. in one hour (no E.S.R. done on first admission). On May 28 a blood count showed: haemoglobin, 13.3 g.% (90% Haldane); red cells, 4,400,000 per c.mm.; white cells, 6,600 per c.mm.; haematocrit, 42%; mean corpuscular volume, 96 μ^3; mean corpuscular haemoglobin concentration, 32%; normal film. Liver-function tests: serum bilirubin, normal; thymol turbidity, 4 units; alkaline phosphatase, 7 units per 100 ml.; plasma proteins—albumin 5.6 g.%, globulin 2.4 g.%, total 8 g.%; bromsulphthalein, normal (no retention of dye). The Wassermann reaction was negative.

Animal Inoculation.—After the urine had been made alkaline to litmus a guinea-pig was inoculated intraperitoneally with 2 ml. of the centrifugalized deposit (33rd day of illness). The animal remained well and was sacrificed 22 days later: no leptospires were seen by direct microscopy and none were isolated by culture. Failure to isolate the organism was probably due to the fact that the guinea-pig is not highly susceptible to infection with *L. canicola* (Mackay-Dick and Watts, 1949; Whitehouse, 1952, and others). Also, the patient's premature departure prevented the collection of a urine specimen at the optimum time. The patient had earlier received several injections of penicillin, which may have been lethal to the leptospires.

Summary

The occurrence of a case of canicola fever in Ireland is reported. Infection was probably by dog's urine. The case presented characteristic clinical features—namely, abrupt onset with rigors, muscular pain, headache, photophobia, and gastro-intestinal and renal upset. Jaundice was absent. Recovery was rapid.

We wish to thank Dr. J. C. Broom, of the Wellcome Research Institution, London, for his advice and for carrying out the cross-absorption test. We are indebted to Dr. A. H. Diamond for his help with the early clinical details, and to Dr. Mary Uprichard, resident medical officer, Belfast City Hospital, for her painstaking work on the case. Acknowledgment is also due to Dr. V. D. Allison, Director of Laboratory Services, Northern Ireland Hospitals Authority, for his interest in the laboratory work.

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TWO EXAMPLES OF THE -D-/-D- GENOTYPE IN AN AMERICAN FAMILY

BY

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This report deals with unusual findings in both the red blood cells and serum of a 48-year-old white woman (Mrs. V. W.) suffering from tuberculosis. In 1940 she received one bottle of blood following the first stage of a thoracoplasty. No transfusions were required for the two operations performed several months later. In May, 1952, she submitted to partial lobectomy, during which procedure four bottles of blood were administered. Eight days after the operation her serum was found by one of us (O. B. B) to be incompatible with 72 random Group O bloods. The only blood found to be compatible was that of the patient's brother, J. C.

The Red Cells of Mrs. V. W.

The blood groups of the patient (Mrs. V. W.) are: O, NsNs, P+, Lu(a−), kk, Le(a− b+), Fy(a+), Jk(a−), Tj(a+), and Mi(a−); the blood groups of her brother (J. C.) are the same save that he is MNSs and Jk (a+). Only the Rh grouping presented any difficulty.

The red cells of Mrs. V. W. and of her brother were strongly agglutinated by anti-D sera; though not agglutinated by anti-c sera they were only weakly agglutinated by a powerful anti-C serum. The clue to the situation was revealed when it was found that saline suspensions of both samples of red cells were agglutinated by incomplete anti-D. This called to mind the remarkable case of Mrs. B., whose genotype was -D-/-D- (Race, Sanger, and Selwyn, 1950, 1951).

Subsequent investigation showed that the Rh genotypes of Mrs. V. W. and of her brother were indeed -D-/-D-. Saline suspensions of the two samples of red cells were agglutinated by three complete anti-D sera, by 14 incomplete anti-D sera, by five anti-C sera which also contained incomplete anti-D, and by one anti-E serum which also contained incomplete anti-D.

*Dr. R. K. Waller has died since the completion of this report.

Saline suspensions of both samples were *not* agglutinated by one anti-C serum free from incomplete anti-D, five anti-E sera free from incomplete anti-D, five anti-c sera, three anti-e sera, one anti-C^w serum, and three samples of incomplete anti-D. Neither sample of red cells reacted with two incomplete anti-C sera free from incomplete anti-D (from Rh-positive donors). Neither sample reacted with the serum of the original -D-/-D- patient, Mrs. B.: this serum had agglutinated all of more than 1,400 samples of Group O red cells, and was shown to contain anti-C, anti-c, and anti-e (Race, Sanger, and Selwyn, 1950, 1951).

Saline suspensions of red cells of the original -D-/-D- patient, Mrs. B., had been agglutinated by 14 out of 16 incomplete anti-D sera. Dr. Philip Levine, of Ortho Research Foundation, has tested saline suspensions of the red cells of Mrs. V. W. against titrations of 13 incomplete anti-D sera; the results are shown in the Table; the cells were agglutinated by 11 of the 13 sera. The agglutination of these cells, however, is not directly related to the titre of incomplete anti-D, as is indicated by the striking differences observed in the behaviour of the five sera of highest titre. Dr. Levine showed that the absence of C from the red cells of Mrs. V. W. could also be demonstrated with the aid of a complete anti-D + anti-C serum; he found that the anti-D component could be successfully blocked by the addition of selected incomplete anti-D (see Table).

Differences in Behaviour of Various Anti-D Sera. Tests by Dr. Philip Levine with 13 Sera Containing Incomplete Anti-D

Titre	No. of sera	Titration with cells of Mrs. V. W. in saline
1/4	1	1/2
1/8	1	1/1
1/16	1	1/8
1/32	1	1/2
1/64	3	1/4, 1/4, 1/64
1/128	1	1/4
1/512	5	0, 0, 1/2, 1/128, 1/256

The Serum of Mrs. V. W.

The serum of Mrs. V. W. has reacted with all of approximately 250 unselected samples of Group O red cells so far tested; it does not react with those of her brother J. C. or with those of Mrs. B. The serum reacts only weakly with cells suspended in saline but strongly by the indirect antiglobulin, the albumin, and the trypsin methods.

Titration of the serum of Mrs. V. W. showed values of 1/128 to 1/256 with the indirect antiglobulin test. Titration with bloods of various genotypes failed to reveal direct evidence of a mixture of antibodies. Absorption experiments now being done present considerable difficulties because of the small quantities of serum available and a gradual diminution of titre in more recent bleedings. So far only anti-e has been isolated, after absorption with cDE/cDE red cells. In view of the parallelism with the blood of Mrs. B. it is very likely that the high incidence of positive reactions is due to the presence of antibodies for both C and c and perhaps E as well as e. Under such conditions all bloods would be incompatible except those with the identical genotype -D-/-D-. No atypical antibodies could be demonstrated in the serum of the compatible sibling, J. C.

As in the case of Mrs. B., there is a history of cousin marriage: the parents of Mrs. V. W., each of whom must have contributed the chromosome -D-, were first cousins. Efforts are being made to trace any consanguineous relationship between the British and American families. Further studies are planned on three additional surviving siblings, five others having died—three from tuberculosis, one from influenza, and one from accidental causes.

It may be that the chromosome -D- is not as rare as it was first thought to be; it may, for example, be no rarer than the chromosome CdE. In the heterozygous state the chromosome -D- would usually escape detection, though it can be recognized if it is specially sought for (Race, Sanger, and Selwyn, 1951).

Summary

Two further examples of blood representing the Rh genotype -D-/-D- are described. The samples come from a white American woman and her brother, offspring of a first-cousin marriage.

The sister has had five blood transfusions. Her serum is incompatible with all of about 250 unselected samples of Group O blood, but it is compatible with her own red cells, her brother's, and with those of the original -D-/-D- British patient. Of the several antibodies which are doubtless present only anti-e has so far been identified. No unusual antibodies could be found in the serum of the brother.

The red cells of the two Americans are the only samples so far found to be compatible with the serum of the British patient, besides her own, though more than 1,400 samples have been tested.

We wish to thank Mrs. V. W.'s physician, Dr. I. N. Hunnicutt, of Virginia, for his active help in this investigation.

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Medical Memoranda

Uterine Chorionepithelioma

The possible development of chorionepithelioma following hydatidiform mole is well recognized, although there is a wide variation in estimates of the incidence of the malignant change. In the follow-up of cases of hydatidiform mole the biological tests for the excretion of gonadotrophin in the urine occupy a prominent position, but the interpretation of their results presents problems which are not widely enough understood, despite the excellent summary by Brews (1950). The following case illustrates the difficulty of diagnosis when the Aschheim–Zondek reaction is only weakly positive.

Case Report

The patient, a 1-para aged 32, had had an uneventful pregnancy three years previously. Her last menstrual period began on February 1, 1950, and very early in the pregnancy she attempted to procure a miscarriage by taking a large dose of quinine. At the ninth week of amenorrhoea vaginal bleeding occurred and the case was treated as one of threatened abortion. It was noted at this time that the uterine enlargement corresponded to that of a 12-weeks pregnancy. The diagnosis of hydatidiform mole was made at the eleventh week, when the fundus of the uterus had arisen to midway between the pubic symphysis and the umbilicus. At this stage the early morning urine gave a positive Aschheim–Zondek reaction in a dilution of 1 in 10, but was negative at 1 in 100.

Vaginal evacuation of the uterus was effected on April 22 after dilatation of the cervix by laminaria tents. The tumour removed was a typical hydatidiform mole with characteristic microscopical appearance. There was no evidence of malignancy in the sections. Twenty days later the uterus had involuted satisfactorily and the Aschheim–Zondek reaction had become negative. But further biological tests were made at intervals, and 57 days after evacuation it was found that the Aschheim–Zondek reaction was again positive, though negative in dilution.

The patient was readmitted to hospital and examined under an anaesthetic on July 7. The uterus was bulky, the cavity measuring 3¼ in. (9.5 cm.), and the left ovary was

slightly enlarged. With a ring forceps, fragments of apparently typical hydatidiform mole were removed, and then a curettage was performed. Microscopy revealed considerably more trophoblastic activity than in the original specimen, with variations in nuclear size and density, and occasional mitoses. No villi were seen in the curettings. Some bleeding persisted, and one week later the Aschheim–Zondek reaction was still positive, though remaining negative in dilution. *X*-ray examination of the chest showed no abnormal shadows.

In view of the recurrence of the mole with atypical trophoblastic activity, total hysterectomy with bilateral salpingo-oophorectomy was performed on July 21—that is, 91 days after evacuation of the mole. Both ovaries contained small luteinized and atretic follicles; in the right ovary there was also a recently ruptured small lutein cyst. The uterus was bulky and contained a haemorrhagic tumour approximately ½ in. (1.3 cm.) in diameter near the right cornu. The growth extended from the endometrium through approximately half the thickness of the uterine wall. Microscopically the growth was a typical chorionepithelioma with malignant trophoblastic elements invading the myometrium. Sections of the ovaries and uterine tubes revealed no secondary deposits.

The patient's progress was uneventful; at examinations 7 and 16 weeks after operation there was no clinical evidence of recurrence, and on each occasion the Hogben test was negative. Subsequent direct follow-up has not been possible, as the patient went abroad, but a letter reports that she was well in January, 1952.

COMMENT

In 1939 Brews observed that as a method of absolute diagnosis of active chorionepithelioma quantitative hormone assays had failed to realize initial expectations. By that time cases had been reported in which the biological tests for urinary gonadotrophin had remained negative in the confirmed presence of a tumour. Cuscaden and Bettinger (1940), in describing a case in which certain features closely resembled that now reported, refer to the possible fallacies of the biological tests and maintain an attitude of great caution in accepting reports of cases of chorionepithelioma without a positive Aschheim–Zondek reaction. The possibility of a negative pregnancy test in the presence of chorionepithelioma is mentioned by Baird (1950) and Browne (1950), while Sutherland (1951) has collected 19 reports of such cases from the literature, and Richli (1950) describes another in detail.

In trying to explain the negative and only weakly positive reactions the factors to be considered include haemorrhage, necrosis, thrombosis, and fibrous reaction; all of these may separate the tumour from healthy maternal tissue and so limit the absorption of gonadotrophic hormone. Browne (1950) suggests that the degree of anaplasia present in the cytotrophoblast may determine the strength of the Aschheim–Zondek reaction. Sutherland (1951) attempts to relate the very weakly positive reaction to an almost complete absence of syncytium, although he admits that this is not in accordance with the experimental evidence of Jones, Gey, and Gey (1943), who found that the Langhans cells were apparently responsible for the production of chorionic gonadotrophin.

The cases described by Browne (1930), Ehrhardt and Bureck (1939), Scott (1939), and Brews (1950) illustrate the dangers of waiting to establish a firm histological diagnosis in the presence of a persistently positive pregnancy reaction after evacuation of a hydatidiform mole. When the reaction has become negative soon after expulsion of the mole, and later in the absence of a new pregnancy it again becomes positive, radical treatment is indicated. This view, however, is not shared by Siegler, Ravid, and Tobin (1950), who, in presenting a review of 12 cases of chorionepithelioma and acknowledging the fallibility of the biological tests, advise that, "so long as the titre is decreasing or at least remaining constant, watchful conservatism may still be applied." Such a recommendation appears highly dangerous, bearing in mind the fatal cases of Brews and of Ehrhardt and Bureck, referred to above.

Shively (1950) assesses the reliance to be placed upon quantitative urinary gonadotrophin determinations by saying that, because of the variations encountered, they should be used only as confirmatory evidence in the diagnosis of these neoplasms and should not be regarded as necessary diagnostic criteria.

Publication of this case report has been approved by the Director-General, Army Medical Services.

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Traumatic Encephalopathy from Boxing

The risk of serious intracranial damage occurring in boxing is well known, and the following account may be of interest to those concerned with the welfare and medical examination of boxers.

CASE REPORT

A miner aged 26 had boxed on numerous occasions since the age of 15 and as a professional from the age of 20. An ample history, obtained from various sources, failed to reveal evidence of previous mental disorder or any other abnormality, except a minor degree of mental dullness indicated by his school work and Army records. His I.Q. was reported to have been 90 on the Stanford–Binet scale (Form L) when he was tested at some unspecified time before leaving school at the age of 14.

Two years ago, after becoming cruiser-weight champion of his area, slight changes in character became apparent, shown in the form of egocentricity and of monopolizing the conversation with accounts of the various opponents whom he had knocked out. Soon he was knocked out himself after only 18 seconds in the first round, and three months later, in an encounter with a boxer thought by all to be inferior, he took so much punishment that the fight was stopped in the fourth round. His friends were now finding him more quarrelsome and garrulous; he often complained of headaches, and he expressed mild paranoid ideas about his wife which eventually resulted in his admission to a mental hospital a year ago, after he had made threats to kill her with the carving-knife.

He was then found to be slightly confused, was alternately excited or unduly reticent, and had also a slight spatial and temporal disorientation, misidentification of persons around him, confabulation with an associated patchy memory defect for events of the preceding four months, and fleeting olfactory hallucinations. Abnormal physical signs were slurred speech, absent abdominal reflexes on the left side, and a slightly ataxic gait of cerebellar type. The cerebrospinal fluid and an *x*-ray film of the skull were normal.

Gradual improvement took place over a period of six months with sedation and rehabilitation, and he was then

discharged from hospital and obtained work as an unskilled labourer. Residual signs then were amnesia for events over a period of one to two weeks at the time of his last two fights, and what appeared to be a reduction in intellectual capacity. His I.Q. on the Stanford–Binet scale (Form L) was 65. On Raven's progressive matrices and on Kohs's blocks test he was at the 5 percentile and on the Mill Hill vocabulary scale at the 10 percentile level. There were now no abnormal signs neurologically. The E.E.G. showed reduced activity in all leads.

COMMENT

The difficulties in the diagnosis of this type of case have been summarized by Bremner (1950) and one has to admit that the difference in the I.Q. may be wholly or partly due to other factors, and also that further improvement might have been found had examination at a later date been possible.

One hesitates to go as far as Carroll (1936), who believes that every knockout is likely to cause irreparable damage, although the boxer intellectually below average is more likely to show persistent clinical abnormality. A further difficulty is the fact, as observed by Jokl (1941) and others, that severe cerebral injury may occur without anything unusual being observed by spectators at the time, and medical elimination of a contestant in such circumstances may be strongly opposed. Romino (1949) puts forward various suggestions to make boxing safer, such as equality of matching, medical records of each fight, and no fights for three months after being knocked out, to which might be added the use of psychometric tests at intervals and the search for minimal neurological abnormality.

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Comparison of Treatment of Haematemesis by Drip Transfusion of Stored Blood and by Direct Transfusion

The aim of treatment of haematemesis is to produce haemostasis; where a large artery is eroded this can be achieved only by surgery, but haemorrhage from small arteries and veins is stopped by the natural process of vasoconstriction and thrombosis. That repeated transfusions of stored citrated blood may inhibit this natural process, whereas small direct transfusions aid vasoconstriction and thrombosis, is suggested by the histories of the following three cases.

CASE 1

A married woman aged 52 was admitted to hospital on June 24, 1952. She was well until 12 hours previously, when there was a sudden onset of diarrhoea followed by melaena.

On admission her general condition was good, the haemoglobin being 73%. Nine hours later she passed a tarry stool and became pale. Systolic blood pressure was 70 mm. Hg and haemoglobin 44%. A drip transfusion of stored blood was begun, and 3 bottles (each 500 ml.) were given over a period of four hours, followed by 1 litre of normal saline, then 2 bottles of blood at a slower rate. Three hours after the transfusion had finished, haematemesis recurred and the patient became shocked. A surgeon advised medical treatment. A drip transfusion was begun, being continued for two days, during which period further repeated attacks of haematemesis and melaena occurred and 7 bottles of blood and 2 litres of saline were given.

Three days after admission the patient's condition was so low that surgical operation was hazardous, and it was decided to try direct transfusions. Three were given at intervals of approximately four hours, and her condition improved. Twenty-four hours later haematemesis recurred and a drip transfusion of 6 bottles of blood and 1 litre of saline were administered. This transfusion continued over 35 hours, during which period melaena and haematemesis occurred repeatedly.

Her condition was again desperate, and two further direct transfusions were given at intervals of four hours. Although several melaena stools were passed there was no further evidence of severe haemorrhage.

On July 1 the haemoglobin was 48%; two direct transfusions were given to raise the haemoglobin, which on July 15 reached 70%. At this stage a generalized erythematous rash developed, labelled the Stevens-Johnson syndrome, which delayed her discharge from hospital until August 9. *X*-ray examination of the stomach and duodenum was reported as N.A.D. All told, the patient was given 19 bottles of stored blood and 6 direct transfusions.

CASE 2

A man aged 36 was admitted to hospital on December 27, 1951, suffering from haematemesis and melaena.

On admission he was in a shocked state, and a drip transfusion was begun; 4 bottles of bank blood were given, and his condition improved. Within nine hours further haematemesis occurred, and the drip transfusion was recommenced. During the next five days the transfusion was continued and 29 bottles of blood and 9 litres of glucose-saline were administered. During this period the patient repeatedly vomited blood and passed melaena stools.

On January 3, 1952, he was seen by me. His general condition was very low; systolic blood pressure was 90 mm. Hg and haemoglobin 38%. During a period of two days he was given five direct blood transfusions. His condition improved, and no further bleeding occurred. *X*-ray examination showed no abnormality of the stomach or duodenum. He had been given 34 bottles of blood, 9 litres of glucose-saline, and five direct transfusions.

CASE 3

A man aged 28 was admitted to hospital on March 10, 1951. He was suffering from haematemesis and melaena, which occurred on the day of admission.

On examination his skin was pale and he was in a shocked condition. He was immediately given a transfusion of 4 bottles of stored blood by the drip method. The next day he vomited blood and the haemoglobin was 52%. Another drip transfusion was started, and during a period of 17 hours 6 bottles of stored blood were given; but during the transfusion further haemorrhages occurred and on March 13 the haemoglobin was 42%. Another 3 bottles of stored blood were transfused. On March 14 there was severe melaena, and the haemoglobin was 40%. Two bottles of bank blood were given, but again there was haematemesis.

The patient was seen by me at this stage. Three direct transfusions, each of 500 ml., were given on the 14th, 15th, and 16th. Subsequently there was no further bleeding. On March 24 the haemoglobin was 83%. *X*-ray examination on March 27 showed evidence of duodenal ulceration. He had been given 15 bottles of bank blood and three direct transfusions.

COMMENT

In these three cases severe haemorrhage occurred during the prolonged transfusion of large quantities of stored blood and ceased when fresh blood was transfused at short intervals by the direct method. Further investigation, such as a planned research project, would be necessary to establish the validity of this observation as indicating an untoward effect of stored blood transfusions when given to excess, and the purpose of recording these cases is to suggest that such an investigation would be worth while.

Recent work on blood coagulation and thrombosis emphasizes the importance of blood platelets in the natural

process of haemostasis, and the lack of platelets in stored blood may be of significance.

The direct transfusions were carried out with a rotary pump modified by Julian Smith (1941), and the technique has been previously described (McLean, 1951).

It has been objected that a rapid rate of transfusion, which cannot be avoided by the direct method, may cause further haemorrhage; in practice, however, this has not been observed. Another objection is that cardiac failure may be precipitated. This is possible in patients with severe anaemia and impaired myocardial efficiency, but, during the transfusion, symptoms and signs of circulatory embarrassment are readily observed and can be relieved by a small venesection.

In recent haematemesis, when the blood volume has been reduced, there seems to be little likelihood of causing cardiac failure.

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Incarceration and Sacculation of the Uterus with Rupture of the Cervix

Incarceration of the retroverted gravid uterus producing retention of urine and abortion is common, but the association of sacculation of the anterior uterine wall is rare. The following case is also of interest, as rupture of the cervix occurred during the abortion of an 18-weeks foetus. Rupture of an incarcerated retroverted gravid uterus has been reported before by Campbell (1908). In his case retention of urine occurred at 18 weeks, followed by rupture of the anterior uterine wall during labour at 26 weeks.

CASE REPORT

A primigravida aged 25 was admitted to hospital at 10.30 a.m. on August 5, 1951, as a case of threatened abortion. Her last menstrual period began on April 5, and she was therefore 18 weeks pregnant. The sudden onset of severe intermittent hypogastric pain with backache had occurred 12 hours previously; there had been no vaginal bleeding. She had suffered no serious illnesses or operations, but an attack of cystitis had occurred two weeks before admission.

Examination showed the patient to be very distressed, with pain far in excess of that usually experienced during an abortion. Her temperature was 97° F. (36.1° C.), pulse 104, and blood pressure 140/80; she was pale although not shocked. Abdominal examination revealed generalized hypogastric tenderness, and the uterus was felt at the umbilicus, compatible with a 22-weeks rather than an 18-weeks pregnancy.

Vaginal examination after catheterization showed that the cervix was taken up, softened, and undilated; there was no bleeding. A soft tender cystic mass continuous with the cervix was occupying the pouch of Douglas. The uterus could be felt extending to the umbilicus, but the contour was concave, resulting in the anterior uterine wall lying well behind the symphysis pubis. A diagnosis was made of incarceration of a retroverted gravid uterus with anterior sacculation.

The patient continued to labour with frequent painful contractions, and at 3.50 p.m. a foetus compatible with an 18-weeks gestation was delivered, but the placenta was retained. There was no excessive bleeding or shock. Examination under general anaesthesia at 6 p.m. showed that the external cervical os had failed to dilate and the patient had aborted by rupturing the posterior wall of the cervical canal. The placenta was partly adherent to the posterior fundal wall and was easily removed following digital separation; the uterus was still retroverted, but the signs of anterior sacculation had now disappeared. It was decided not to repair the rupture at this stage, as the partly detached external cervical os was not dilated enough to allow for adequate drainage. Bleeding was controlled by ergometrine, 0.5 mg., given intravenously, and the patient was returned to the ward. She developed a temperature of 101° F. (38.3° C.), but after the administration of penicillin, 100,000 units six-hourly, it returned to normal in 48 hours and remained so until her discharge.

On August 13 examination showed a cervico-vaginal fistula which admitted one finger. The internal os and external cervical os were both closed, although a sound could be passed freely through them; the length of the cervical canal was 1½ in. (3.8 cm.). The uterus was regular in outline and still retroverted, but no other abnormality was detected in the pelvis. Under general anaesthesia the edges of the fistula were excised and the cervical canal was reconstituted with two layers of No. 2 chromic catgut. When the patient was seen on September 25 the cervico-vaginal fistula had largely healed up, but a definite opening ¼ in. (0.6 cm.) in diameter was present in the posterior wall of the cervical canal.

COMMENT

The obvious explanation of the rupture is criminal trauma in an attempt to procure the abortion. Exhaustive questioning, the patient's sincere desire for a family, the absence of bleeding before admission, and the initial vaginal examination made it clear that such a simple solution could be excluded.

Rigidity of the external os may complicate the abnormal uterine mechanism which occurs when retroverted gravid uteri with anterior sacculation abort, and rupture of the uterus or cervix results. An abnormal uterine action in this case is inferred from the excessive pain during labour, and the abnormal polarity of the uterus interfering with the capacity of the cervix to dilate. The downward thrust in anterior sacculation with retroversion centres on the thinned-out posterior cervical wall, and rupture in the weakest portion follows. A misdirection of the uterine axis also occurs in malpositions such as pendulous belly, ventrifixation of the uterus, and sacculation of the uterine wall, and is regarded by Eden and Holland (1948) as predisposing to uterine rupture.

Annular detachment of a rigid cervix is seen occasionally in primigravidae during labour at term, and a similar mechanism probably occurred in this case, with the production of a cervico-vaginal fistula instead of detachment of the external os. Three cases of cervico-vaginal fistula following labour at term have been reported by Finn (1950). In his cases, ischaemia of the cervix followed by necrosis of the anterior cervical lip occurred from disproportion between the vertex and symphysis pubis, and he mentioned that unusually rigid or exceptionally long cervices might also predispose to cervical necrosis. The length of the cervix in our case was excessive, approaching 1½ in. (3.8 cm.), and this is probably the essential factor in the production of the cervico-vaginal fistula.

The fate of the bladder in these cases has been referred to by Munro Kerr and Chassar Moir (1949), who state: "Although bladder troubles occur with sacculation, they are seldom so extreme, nor is there extensive destruction of the bladder wall which is so common an occurrence in the ordinary variety of incarceration of the uterus." Our case supports their view.

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Reviews

CARDIOSCOPY

Cardioscopy. By William Evans, M.D., D.Sc., F.R.C.P. (Pp. 144; 207 figures. £2.) London: Butterworth and Co. 1952.

With the publication of this volume Dr. William Evans may have completed what he has to say about the heart in book form, for *Cardiology* and *Cardiography* (electrocardiography and phonocardiography) have come before; but it is hoped this is not so, for in certain respects he is unexcelled. He is a master of clear expression. No one can doubt what it is that he has said or written. His illustrations are flawless, no matter who publishes them. He always has something interesting to say, a new idea, a new way of looking at a thing, some wholesome heresy, or some obstinate reaction. His views are based almost entirely on his own work and experience, and he so often provides us with fresh evidence.

Cardioscopy is dedicated to Sir John Parkinson; he more than any other in this country appreciated the full value of this method of examining the heart and expounded its intricacies so ably. It had been hoped for a long time that Sir John himself would write this book, either alone or with another of his disciples, Dr. Evan Bedford. But, since he has chosen not to do so, we are grateful that the task has fallen to the lot of William Evans.

He has met the obligation nobly. The book is really an atlas with a running commentary. It is concise, accurate, and orthodox, and the illustrations are outstanding. Cardioscopy does not include angiocardiography, and it is well to be reminded so forcibly how much information the simpler radiographic technique can give.

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MODERN ELECTROCARDIOGRAPHY

The Unipolar Electrocardiogram: A Clinical Interpretation. By Joseph M. Barker, M.D., F.A.C.P., assisted by Joseph J. Wallace, M.D., F.A.C.P. Foreword by Frank N. Wilson, M.D., F.A.C.P. (Pp. 655; 458 figures. No price.) New York: Appleton-Century-Crofts, Inc. 1952.

Modern Electrocardiography Volume I. By Eugene Lepeschkin, M.D. The P-Q-R-S-T-U Complex. Foreword by Frank N. Wilson, M.D. (Pp. 598; 91 figures. £4 11s. 6d.) London: Baillière, Tindall and Cox. 1951.

The Unipolar Electrocardiogram is a handsome volume, very well produced. The many illustrations are faultless. The title would lead the reader to suppose that but little would be heard of the bipolar standard leads, except perhaps at the end for antiquarian interest; more particularly so because at the beginning there is a fine portrait of F. N. Wilson (who contributes a pleasant foreword) standing by a blackboard on which is drawn Einthoven's triangle: at this he is gazing with a look of doubt and disapproval. One would have thought that the arrhythmias would hardly find a place here, although it is true that VF or V_1 usually shows auricular activity very well. There is nothing peculiar in the use of unipolar leads in the study of this subject, and the book would have been shortened by omitting two chapters in which many of the illustrations are not unipolar at all. The account of the physical basis of electrophysiology is remarkably clear, but the account of the current of injury is less so. The electrical positions of the heart are well explained. In the chapter on bundle block the words "intrinsic" and "intrinsicoid" seem to be used synonymously, although their different meaning is explained elsewhere; perhaps this will confuse the reader. The chapter on infarction is full and clear. The author is sceptical about the value of exercise tests in the diagnosis of cardiac pain. The type is good; special importance is shown by heavier type. This is a most comprehensive survey, almost too full, but a valuable mine of information.

The first volume of *Modern Electrocardiography* is on the P Q R S T U complex. The scope of the material it contains can be estimated by the number of references, in all 9,999—but the last one is lost. What is one among so many? It is unfortunate that the streams of these four-figure numbers along the lines of the text, sometimes a dozen or more, for the best part of two lines of print, make the matter almost unreadable. But the author points out that this book is really a summary, concise and comprehensive, of all electrocardiographic knowledge that has accumulated since 1933, when F. N. Wilson (who contributes a foreword) "instituted a new era of scientific thinking in this formerly largely empirical discipline." There is a chapter on the electrocardiogram of animals, an interesting novelty. The effects of physiological, physical, and pharmacological agents have each a chapter. The effects of ventricular strain and hypertrophy are discussed. Myocardial infarction gets only 40 pages and coronary insufficiency 16; it would seem that there is some lack of proportion here, for 266 pages are devoted to the normal. But this is a remarkable compilation which will supplement other books and will be a most useful source of reference that the cardiologist can hardly be without. Illustrations are few and mostly good. The print is excellent, and the varying founts of type indicate the relative importance of subjects. The numeration of paragraphs helps one to find them.

TERENCE EAST.

SURGERY OF THE COLON

Die Chirurgie des Dickdarms. By Professor Hans Finsterer. (Pp. 382; 19 figures. $12.50.) Vienna and Düsseldorf: Wilhelm Maudrich. 1951.

The surgery of the large intestine is a difficult and complex subject. There is no region of the body in which the surgeon is confronted with problems more awkward or which may cause him greater anxiety. The appearance of such a work as this, based on the vast experience of one of the greatest surgeons of our time, is one which will be widely welcomed, and we hope that an English translation may soon be brought out to render it available to a wider circle of readers.

Professor Finsterer has covered the whole subject with the utmost thoroughness, and he gives full accounts of the cases on which his more important conclusions are based. In the opening chapters he gives precise details of operative work, from caecostomy to total colectomy, and of the special precautions which are required in this region. There follows a chapter on chronic constipation, to which he has plainly devoted great attention and in which he reaches the mature if unusual conclusion that in suitable cases the correct treatment is a *left*-sided hemicolectomy.

Acute inflammations, including acute appendicitis, are fully discussed, and there follows an excellent account of both acute and chronic colitis, and of diverticulitis. A brilliant article on carcinoma concludes a work of unusual value. It represents an experience which must be almost unique, presented with the fullest detail and the utmost clarity. We regret that owing to the exigencies of the time there are not fuller illustrations, and most of all that there is so far no English translation.

HENRY SOUTTAR.

A TEXTBOOK OF PAEDIATRICS

The Child in Health and Disease. A Textbook for Students and Practitioners of Medicine. By C. G. Grulee, M.D., and R. C. Eley, M.D. Second edition. (Pp. 1,255; 304 figures. £5 14s.) London: Baillière, Tindall and Cox. 1952.

This large volume is the second edition of a treatise that enjoys a considerable reputation. It is the work of 87 authors, distinguished for their contributions to paediatrics and allied subjects, and they deserve congratulation for their industry in producing, under the leadership of Grulee and Eley, a reference book of much merit. It is only natural that the chapters should vary in quality and that there

should be some lack of proportion between the different sections, for these disadvantages seem to be unavoidable when the team of authors is so large. But the reader will not fail to realize and appreciate the enthusiasm and hard work that have gone to the making of the book. In this edition appear new chapters on adoption, cardiovascular surgery, pancreatic fibrosis, viral hepatitis, haemolytic disease (erythroblastosis foetalis), and the medical supervision of summer camps. Adolescence—a subject that often receives inadequate attention—is competently described, and there is a useful article on paediatric procedures.

It would be a great help to the reader if the index could be improved in the next edition, and cross-references in the text would also be welcomed. When authors are quoted there should be special care that their names are correctly spelt in the list of references. Many of the illustrations serve their purpose well, but a number (for instance, on pp. 458, 461, 483, and 485) are not good enough. The book is well produced, and will be a valuable addition to medical libraries, especially for postgraduates.

NORMAN B. CAPON.

AMERICAN EPIDEMIOLOGY

The History of American Epidemiology. By C.-E. A Winslow, Dr.P.H., Wilson G. Smillie, M.D., James A. Doull, M.D., John E. Gordon, M.D. Edited by Franklin H. Top, M.D. (Pp. 190. £1 16s.) London: Henry Kimpton. 1952.

The chapters of this book, written by four leading American epidemiologists, are expansions of their papers presented at the Twentieth Anniversary Session of the Epidemiology Section of the American Public Health Association held in New York City on October 27, 1949. The authors and the editor, in paying tribute to the pioneer work and doctrine of epidemiologists on this side of the Atlantic, express some doubt about the extent of the contribution which their countrymen have made to the sum total of knowledge in this field. The account of epidemiological researches here given, and the many illustrious names cited—Benjamin Rush, J. S. Billings, C. V. Chapin, Theobald Smith, Milton J. Rosenau, for example—clearly prove that there is ample material for a much larger work on American epidemiology, to which this little book would form the best of introductions.

Professor Winslow writes the history of the colonial era, when the wrath of God and miasma were both held responsible for epidemics of yellow fever, cholera, typhoid, and malaria, and doctors disputed (as they do in our own day) about Sydenham's "epidemic constitution" and contagion. Noah Webster, better known for his dictionary, was interested in the problem. He collected essays and letters from ten physicians, and in 1799 published a two-volume work on the *Epidemic and Pestilential Diseases* which sided with the anticontagionist majority. It is an admirable summary of the state of knowledge of the time. Professor Smillie describes the period of great epidemics in the United States (1800–75), though in so brief a space he can hardly do justice to them all. The same criticism applies to Professor Doull's chapter on the bacteriological era (1876–1920). There is only a brief reference to industrial hygiene, which the co-operation of public health experts and employers of industry have so greatly advanced in the United States. Of special interest, though incomplete, are the long list of American contributors to the aetiology of microbiological diseases, and the work of Flexner and others on healthy carriers of disease. Concerning progress in professional education (p. 83), it might have been mentioned that Welch secured the help of Sir Arthur Newsholme in planning and developing the School of Hygiene and Public Health at Johns Hopkins University. It is stated that the first epidemic of anterior poliomyelitis to be described in the United States occurred in Rutland, Vermont, in 1894, but George Colmer (*American Journal of Medical Science*, 1843, p. 248) mentions an earlier outbreak in West Feliciana, Ind., in the fall of 1841, and the disease possibly occurred in Albany in 1795.

The concluding chapter, "The Twentieth Century—Yesterday, To-day, and To-morrow," is from the pen of Professor John E. Gordon, who came as epidemiological ambassador from Harvard to help the Ministry of Health with his wisdom and friendship in the early days of the war. Readers will enjoy his masterly analysis of modern epidemiology, which he points out "should escape its still too common restriction to communicable diseases to find application in organic diseases of non-infective nature, in mental disorder, and in the problems associated with trauma."

ARTHUR S. MACNALTY.

THE PSYCHIATRIST AS WITNESS

Forensic Psychiatry. By Henry A. Davidson, M.D. (Pp. 398. $8.) New York: The Ronald Press. 1952.

The contrasting attitudes of the psychiatrist towards his patient and of the lawyer towards his or another lawyer's client have their origin in the different objectives of the training for each profession and their very different professional usage. When two interpretations of the same evidence are seriously at variance, lack of an adequate common language often militates against mutual understanding. The lawyer often rails with good reason against the speculative explanation and excess of terminology of the psychiatrist who has been temporarily translated from the consulting-room to the court, and the latter is apt to deplore the lack of interest shown by lawyers in abstract values and the complexities of human motive. Judgment of right and wrong plays no great part in the normal relationship between doctor and patient, but it underlies the whole procedure of the criminal court, and the psychiatrist who is only an occasional visitor must adapt himself to its strange conditions if he is not to be demonstrated in cross-examination to be a vague creature who uses his *expertise* to introduce complexities where none existed before.

Dr. Davidson, as the result of long experience as an expert witness and a full appreciation of the legal point of view, is able not only to give clear-cut guidance on how to examine the patient, write the report, and answer cross-examination, but to make a real contribution towards a common language between the two professions. It is unfortunate, therefore, that the differences in procedure between British and American courts are so great that only the sections on general principles will be of use to psychiatrists in this country. The schemes for the examination of patients for different legal purposes are, however, of great value and could readily be adapted to British usage.

The differences in the penal codes, and the persistence in some States of immature, prejudiced, and somewhat experimental legislation as revealed in this book, are of great interest, as are the great variations in such matters as the power of the juvenile courts, the control of adoption, and the evidence necessary to establish the fact of intoxication. Psychiatrists in the United States are fortunate in having such a guide, but its use as a handbook for the expert witness in Britain is considerably limited by its local application.

ALEXANDER KENNEDY.

Love of the strange and rare, which sends some people to the zoo on Sunday afternoon and makes others concentrate on the small type in textbooks, is as prevalent in our own profession as elsewhere. And doctors whose taste for rarities is still unsullied by frequent contact with the commonplace will find something of interest in the latest collection of papers by Dr. Parkes Weber (and collaborators) entitled *On Naevi and Miscellaneous Subjects* (London: H. K. Lewis. 12s. 6d.). The "miscellaneous subjects," which comprise eleven of the twelve papers, include reports on unusual disorders of the skin, bone, and nervous system, and some notes on Osler indicating that he shared Parkes Weber's interest in uncommon syndromes. The book concludes with a neat lecture on epigrams—laudatory, sceptical, and critical—on medical themes.

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EPIGLOTTITIS AND LARYNGOTRACHEOBRONCHITIS

One of the many childhood conditions included under the term "croup" is laryngotracheobronchitis. Little was written about this condition until a few years ago, but there have been several important publications about it in the last decade. Increasing knowledge has inevitably led to attempts at classification—according to the aetiological agent, clinical picture, or anatomical site of the infection. Rabe[1] divided 347 cases of "infectious croup," seen at New Haven, U.S.A., into three types, which he thought presented quite well-defined clinical pictures. The first comprises those cases due to *C. diphtheriae*, and the second those in which no organism was isolated. He thought that these were probably due to a virus, and termed them "virus croup," but there is little evidence that these are cases of virus infection. The third type comprises those due to *Haemophilus influenzae* Type B. The diphtheritic type will not be considered here, but its occurrence must always be borne in mind.

In the group termed by Rabe the "virus" form there is usually a history of infection of the upper respiratory tract, for one day to three weeks, before "croup," in the form of hoarseness and stridor, develops. When the child is admitted to hospital there is stridor, often inspiratory and expiratory, with a rapid respiration rate and varying degrees of intercostal recession. The constitutional upset varies from child to child. Some are acutely ill, though the child is rarely profoundly "toxic" in appearance. He may be cyanosed, and the temperature and pulse rates are raised, often considerably so. Rhonchi constitute the only adventitious sign found on auscultation of the chest, but it is not always easy to be sure of this when stridor is severe. In cases presenting severe laryngeal obstruction there is a general reduction of air entry. The throat may or may not be inflamed, but there is nothing characteristic about its appearance. Exudate is unusual. Soreness of the throat is not an important symptom, if present at all. The white-cell count is often normal. Rabe found that the most frequent and severe complication was some form of extra-alveolar air—mediastinal emphysema or pneumothorax. Others do not appear to have mentioned these complications.

Probably most of the cases described recently in this *Journal* by Briggs and Heseltine[2] and Emery[3] were of the "virus" type. Briggs and Heseltine showed that in 37 of their 39 cases the chief danger lay in obstruction of the small bronchi and terminal bronchioles by viscid secretions, which were liable to suffocate the child. Emery, in a careful study of 35 fatal cases in Sheffield, some of them referred to him by the coroner on account of unexplained sudden death, found tenacious grey material in the lower trachea and bronchi in 18. He thought that death in most of these children was due to mechanical suffocation by abnormal mucous secretion. Four of the 39 patients described by Briggs and Heseltine died, all of them because of this mechanical obstruction.

Of Rabe's 347 cases, 28 belonged to his third type of infectious croup—that due to *H. influenzae* Type B. In these cases there was a history of severe sore throat, with the extremely rapid development of obstruction to breathing. And there were high fever and signs of "shock" or severe toxaemia, associated often with an ashen grey pallor, out of all proportion to the duration of the illness. The history in all these cases was very brief. A third of the children had tender cervical lymph nodes. In each case laryngoscopy showed supraglottic oedema, with a markedly swollen, acutely inflamed epiglottis. The inflamed epiglottis could often be seen by simple tongue depression. Oedema of the cords was unusual. *H. influenzae* Type B was recovered from the blood culture in all but three, and from the nasopharynx in all but one. There was usually a polymorphonuclear leucocytosis, the white-cell count averaging 23,000 per c.mm.

Similar cases have been described by several workers in America, and more recently in this country by Camps at the Royal Society of Medicine in December last year. Miller[4] described 12 cases, all due to the *H. influenzae* Type B. Neffson[5] described a similar picture, but thought that organisms other than *H. influenzae* Type B could cause it, including the haemolytic streptococcus. Neffson drew particular attention to the character of the stridor in the two conditions. He describes the stridor in laryngotracheobronchitis, in which the lesion is glottic or subglottic, as a croaking sound in early cases; in later cases, with increasing oedema, the stridor becomes high-pitched and muffled. In epiglottitis, however, the sounds are different and

1 *Pediatrics*, 1948, **2**, 255, 415, 559.
2 *British Medical Journal*, 1952, **2**, 1064.
3 Ibid., 1952, **2**, 1067.
4 *Laryngoscope*, 1948, **58**, 514.
5 *Acute Laryngotracheobronchitis*. New York: Grune and Stratton. 1949.

pathognomonic. When the child is awake there is a low-pitched inspiratory stertor in the early stages, with a louder and lower-pitched coarse expiratory rattle, resembling a snore. Later, when oedema is marked, the inspiratory stertor is replaced by a somewhat muffled high-pitched stridor, or the inspiratory stridor disappears, the expiratory component remaining unchanged. He emphasized that these were dry sounds and had to be distinguished from the "ruttling" produced by mucus. If the epiglottis could not be seen by tongue depression or laryngoscopy, or if laryngoscopy was thought inadvisable, a lateral radiograph of the throat was sometimes useful in showing the narrowing and obstruction of the airway above the vocal cords. Camps described similar cases in Britain, but *H. influenzae* Type B was recovered in only two, though in the earlier cases seen by him this organism was not specifically looked for. The mortality in these cases is quite high. In Rabe's series it was 18%.

The treatment is basically the same for both types —the relief of anoxia, the provision of an airway, and the combating of infection. Humidification of the atmosphere by a steam kettle or aerosol vaporizer seems to be beneficial. Briggs and Heseltine, in common with other workers, strongly advocate that tracheotomy should be performed as an elective procedure, not as a last desperate measure in a moribund child. If the child with restlessness and severe stridor does not rapidly respond to rest in bed, or if there are cyanosis, extreme fatigue, increasing restlessness, pallor, and stridor, with decreasing air entry, tracheotomy should be performed without delay. In the "virus" type this is essential to secure an airway, and to enable the thick tenacious secretions, which are the principal cause of death, to be sucked out of the bronchi. For this purpose they found that an electrical sucker with polythene tubing was needed: the water suction apparatus was not adequate. Rotation of the head combined with twisting of the curved tubing allowed easy passage of the tube into either main bronchus, and down distally to a distance of 4 to 6 in. (10 to 15 cm.) in a child aged 3 to 6 months. Suction was repeated in most cases every three to four hours on the first post-operative day. A soft rubber catheter was used to keep the tracheal tube clear of mucus. They emphasized that a special nurse is essential for each child, that the patient should not be hidden in a canvas tent, and that lighting at night should be adequate for inspection of the child. If there is sudden deterioration, the nurse is told to remove the inner tube immediately and apply suction to the outer tube while another nurse sends for medical help. They thought that intubation or bronchoscopy should be an emergency procedure only: repeated bronchoscopy would do more harm than good by damaging the inflamed cords. Of Rabe's 347 cases, 35 (12%) required tracheotomy. Of the 39 cases described by Briggs and Heseltine, 9 needed it.

The use of antibiotics is strongly advocated by many workers, but it is not clear which is the best one to use. Penicillin is undoubtedly effective in many cases, but *H. influenzae* Type B is only moderately sensitive to it and is more likely to respond to chloramphenicol, in a dose of 100 mg. per lb. (220 mg. per kg.), or to terramycin or aureomycin, in a dose of 50 mg. per lb. (110 mg. per kg.). In the "virus" type it is probable that only secondary invaders respond to the drug, whichever is used. Some clinicians also give a sulphonamide (such as sulphamezathine). In America type-specific rabbit serum is given for the cases due to *H. influenzae*, but the exact role of this is uncertain, and it is not normally available in Britain. Whatever antibiotic or other "specific" treatment is given, it must always be remembered that the relief of mechanical obstruction is essential, and that death is much more likely to result from suffocation than from the actual infection.

It is clear that "infectious croup," which includes epiglottitis and laryngotracheobronchitis, should be treated with the greatest respect by the family doctor. If there is a sudden onset of stridor, or if there is an insidious onset of stridor which becomes progressively worse, the child should be sent to hospital without delay. Serious harm is done by waiting until the child is cyanosed, has severe intercostal recession, or is otherwise seriously ill before he is sent in. Furthermore, hospitals which admit small children should have an emergency tracheotomy set ready at all times, so that acute emergencies due to laryngeal or bronchial obstruction can be dealt with immediately.

NOTIFICATION OF PUERPERAL PYREXIA

When child-bed fever was a scourge methods were needed of estimating its frequency, investigating its source, and determining how its spread could be controlled. As knowledge of the bacteriology and the modes of transmission of puerperal sepsis increased, there was a decline in the mortality rate in the first 35 years of this century. The introduction of the sulphonamides caused a further rapid decrease in the death

rate, and when this fall had largely lost its impetus the discovery of penicillin and other antibiotics effected a further decline. In Britain a maternal death from sepsis is now a rare occurrence. But the improvement in the mortality rate is not due to chemotherapy alone: better antenatal care, improved methods of prophylaxis, and increasingly high standards of obstetrical and nursing practice have all contributed, and this is reflected in the fact that the mortality from post-abortion infections has not fallen equally with that from puerperal sepsis.

Because of the decline in morbidity as well as mortality, the puerperal pyrexia regulations were amended in England and Wales in 1951, so that any fever of 100.4° F. (38° C.) or more in a woman within 14 days after confinement or miscarriage became notifiable. Under the previous regulations the temperature of 100.4° F. had to be maintained over or recur within 24 hours; the period covered was 21 days, and the first 24 hours after delivery were excluded. One reason given for supplanting these older regulations was that the use of newer drugs reduced the temperature promptly and so prevented an infection from becoming notifiable. This seems peculiar reasoning when it is considered that puerperal pyrexia is not a specific entity like measles or mumps. Moreover, a single innocent spike of temperature is common within 24 hours of delivery and is almost the rule after caesarean section or other operative delivery.

The 1951 regulations were therefore not received without some criticism, and in his health report for 1951 the Medical Officer of Health for Ilford, Dr. I. Gordon, asks some pertinent questions about what is being notified and who is doing the notifying. The object of the regulations is to control infections of the genital tract, but the cause of the pyrexia is not required to be stated on the notification form. Dr. Gordon therefore obtained information on the cause of the fever in 62 of the 65 cases notified to him in the last five months of 1951. In 50 of the 62 cases the fever was unconnected with any genital infection, and in more than half of all the cases it was ascribed to some disorder of lactation. It is possible that in some, perhaps many, of the cases notified the exact cause of the pyrexia was not known but was imputed to engorgement of the breasts. Dr. Gordon also found that in Ilford 89% of the notifications came from hospitals, although only 63% of deliveries took place in hospitals. He reasoned from this that, even though the complicated cases might have gravitated to hospital, the busy family doctor might omit to fill in yet another form, while the hospital officer, more conscious of temperature charts and of regulations, notified every case of pyrexia. Dr. Gordon therefore concluded that, in his borough at any rate, the notification of puerperal pyrexia bore little relationship to infection of the genital tract and could be dispensed with.

It is indeed doubtful whether the notification of puerperal pyrexia still serves the public health purpose for which it was originally introduced. Maternal mortality from puerperal sepsis is now so low in this country that it is no longer a reliable index of the efficiency of the maternity services or of the state of maternal health after confinement. Yet compulsory notification, if less valuable to the community as a whole, may still be of benefit to the individual woman, for it ensures that the midwife, whose statutory period of attendance on the puerpera is 14 days, summons medical aid at the first possibility of infection. But in their present form the regulations do not provide a satisfactory maternal morbidity index, and, as Dr. Gordon points out, may produce inaccurate statistics, especially in regard to domiciliary confinements. Any system of notification of disease is enhanced in value if the need for flexibility in its application is appreciated. For instance, in the light of present views on the connexion between maternal rubella in early pregnancy and congenital malformations there is much to be said for the compulsory notification of that infectious fever throughout the country. Again, while retaining the present puerperal pyrexia regulations as a rule of the Central Midwives Board, a system of notifying specific complications of labour and abortion, irrespective of the presence of pyrexia and with a more generous time limit, might be useful in evaluating both prophylactic and curative measures in this sphere. Indeed, much could be learnt by making notifiable not only maternal complications such as venous thromboses but also foetal abnormalities the origin of which remain obscure, such as congenital malformations and retrolental fibroplasia. Such notification, if not of purely public health interest, would serve to bring closer together the interests of the community and the interests of the individual.

PROPHYLAXIS OF RHEUMATIC FEVER

It has long been known that the daily administration of a small dose of a sulphonamide, usually sulphadiazine, can be continued without harm for many months, and that it will usually prevent streptococcal throat infection and thus recurrences of rheumatic fever. More recently penicillin has been used for this purpose,

and has usually been given by the mouth. Owing to the very high sensitivity of *Str. pyogenes* of Group A to penicillin the low and variable concentrations resulting from this method of administration are nevertheless enough to keep this organism in check. A course of injections continued throughout the winter is obviously impracticable, particularly in a child, but if the interval between injections could be greatly lengthened this alternative would be worth considering for the increased certainty of its effect. One line of progress has been the development of preparations which in single doses will act for longer and longer periods. One- and two-day effects have been commonplace for some time, but a preparation of which the effect is measured in weeks is now available in N,N'-dibenzylethylenediamine dipenicillin G, known as "bicillin" or benzethacil. The first full account of this substance was given by Elias, Price, and Merrion,[1] of the Wyeth Institute of Applied Biochemistry. Its outstanding property is the very low solubility of only 200 units per ml.: it is also tasteless, which is claimed as an advantage for oral administration. Injected intramuscularly merely as an aqueous suspension a dose of 300,000 units gave detectable amounts in the blood for five days, and one of 2,500,000 units for as long as 15 days. Admixture with a non-aqueous base can prolong these times further, although presumably amounts in the blood will then be lower and perhaps less constant. The first account of work done with benzethacil in this country is published in this issue of the *Journal* (p. 188). The authors of the report, Drs. A. P. Fletcher and C. R. Knappett, have found that the intramuscular injection of an aqueous suspension of benzethacil "gives sustained levels of serum penicillin considerably superior to any repository penicillin preparation yet developed," though in some subjects assayable amounts of penicillin appeared in the serum intermittently.

Several important uses can be thought of for a form of penicillin possessing such remarkable properties, and it is not surprising that among these the possible prophylaxis of rheumatic fever has been studied. Stollerman and Rusoff[2] have administered benzethacil to 143 rheumatic subjects (all but eight being children) for periods of 2 to 10 months. It must be said at once that they obtained no proof of its efficacy in preventing rheumatic fever, since although no recurrences took place in treated subjects there was only one in an untreated patient in the same institution during the period of observation. The drug was injected first in simple aqueous suspension and later in a "polyvinylpyrrolidone vehicle." Patients were given 300,000 units weekly, 600,000 units bi-weekly, or 1,200,000 units monthly, and an extensive series of blood assays showed that each of these systems can be depended on to maintain continuously an assayable level (0.02 unit/ml. by the method used) in the blood of most patients. Some even had detectable penicillin in the blood 40 days after the largest dose. Ten patients on admission and three members of the staff were found to have Group A streptococci in the throat, and daily swabs after an injection of benzethacil showed that the organism disappeared in every case within one day. It reappeared in four days in one patient, and another became a carrier during treatment, but later injections abolished the carrier state in both and no patient had a rise in antistreptolysin titre. The drug was well tolerated, and the results of a study of the penicillin resistance of *Str. viridans* from treated patients' throats suggested that no highly resistant strains were being bred, although comparison with similar studies by another author who gave penicillin orally indicates that both methods may have at least some effect in this direction. It may be assumed with some confidence that infrequent injections of benzethacil will be at least as effective as giving penicillin in moderate doses orally in preventing throat infections. To continue either method of treatment for the greater part of a year must necessarily be costly, and in the choice between them the operation of this factor may well be decisive.

[1] *Antibiot. and Chemother.*, 1951, **1**, 491.
[2] *J. Amer. med. Ass.*, 1952, **150**, 1571.

APES AND MEN

"*Ex Africa semper aliquid novi.*" For some years past the scientific world has become accustomed to learning every so often of the discovery in increasing numbers of fossil higher primates in Transvaal caves. Mr. J. T. Robinson, of the Transvaal Museum, Pretoria, recently announced the discovery at Swartkrans[1] of some remains, including a fragmentary maxilla with some teeth, of *Telanthropus capensis.* The type is apparently transitional between the still ape-like Australopithecinae and undoubted men, such as the *Pithecanthropus* group (including *Sinanthropus*) of Java and North China. *Telanthropus* was hitherto represented only by a mandible, considered by Broom and Robinson[2] to be clearly distinct from the *Paranthropus crassidens* (Australopithecinae) remains obtained at the same site. Dr. K. P. Oakley, of the British Museum (Natural History), is now in the Transvaal in the hope of discovering satisfactory geological and palaeontological evidence on the date of the finds. Meanwhile it is worth considering the possible implications of the new discovery to existing ideas about the course taken by human evolution from the ape stage.

Our nearest living relatives, the great apes, have certain features—among others the "simian shelf" in the section of the mandibular symphysis—which were until recently held to be primitive. The Miocene of Kenya, however, yielded to Dr. L. S. B. Leakey in 1948[3] an almost complete skull of a chimpanzee-like ape (*Proconsul*) without the simian shelf and with other features of skull and dentition more closely resembling the condition seen in man than do those of any of the surviving great apes. It is therefore thought probable that *Proconsul* stands close to the common ancestor of ape and man, and that human and simian stems have pursued separate courses at least since the Miocene, about 15 million years ago.

[1] *Nature, Lond.*, 1953, **171**, 33.
[2] Ibid., 1949, **164**, 323.
[3] Ibid., 1948, **162**, 688.
[4] Zeuner, F. E. *Dating the Past*, 3rd ed. Methuen, London. 1953.

The South African Australopithecinae seem to represent an early branch of the distinct human stem. In brain capacity they were not yet men by any standard that we have learnt to use, but they had already developed the erect posture and possessed a remarkably human type of dentition. Their small brains, prominent muzzles, and enormous jaws and teeth nevertheless betray a not very remote simian ancestry.

The *Telanthropus* mandible was less heavily built. The teeth were large by modern standards, but markedly smaller than those of the Australopithecinae; the mandible lacked some typical australopithecine characters, but showed the beginnings of a mental eminence where none is to be seen in apes or Australopithecinae. The new maxillary fragment enables comparison to be made with those of the Australopithecinae and a modern Bushman. It shows that, in *Telanthropus*, the muzzle was markedly shortened, with reduced procumbence of the upper incisors and a right-angled section at the inferior margin of the nasal aperture instead of the smoothly curving transition between the subnasal region of the muzzle and the floor of the nasal cavity seen in the Australopithecinae. Despite their differences, the remains show other features in common with the Australopithecinae, so that the direct relationship of *Telanthropus* to these can hardly be doubted. Mr. Robinson claims that we have here a form transitional between the Australopithecinae and true hominids, though it would be helpful if we could also know something about the cranial capacity of the new species.

Much hangs on the date which may be assigned to *Telanthropus* and the Australopithecinae. It now appears that it may be necessary to regard them as approximately contemporary. The Swartkrans limestone (travertine) is considered to be late Pliocene. The next evolutionary stage is represented by the *Pithecanthropus* group of fossils, found at the eastern extremities of Asia. If the Transvaal specimens can confidently be dated to the Pliocene (at least one million years ago) it is possible to envisage the further development of the types they represent, their diffusion to the Far East, and their reappearance, perhaps half a million years ago, as the *Pithecanthropus* group. The dating of this group to a period more than 400,000 years ago is based on good palaeontological evidence.[4]

We may then regard the possible steps of human evolution as represented by: *Proconsul*, the Australopithecinae, and *Telanthropus* in Africa: the *Pithecanthropus* group, and the late Middle Pleistocene (about 180,000 years ago) palaeanthropic men of Asia and Europe. Should the Swartkrans finds prove to be only half a million instead of a million or more, years old, as is quite possible, we should be obliged to seek for the Far Eastern *Pithecanthropus* fossils some progenitor other than the Australopithecinae or *Telanthropus*.

Whatever the outcome of further investigations into the dating of the particular specimens concerned, their interest will remain paramount for students of human evolution. Morphologically the Australopithecinae represent an evolutionary stage which would readily be acceptable as essentially Pliocene, and therefore potentially a direct forerunner of the *Pithecanthropus* stage. Even if it should prove that the individuals known to us are late survivals, they must resemble more or less closely earlier members of their species or genus, who could have been the ancestors of *Pithecanthropus*, thus bridging the gap between undoubted apes and undoubted men.

PSITTACOSIS

It has long been known that human beings are susceptible to an infectious disease of parrots, which was given the name psittacosis. The disease is caused by infection with a virus, and in addition to birds of the psittacine group—which includes parrots, cockatoos, and budgerigars—canaries, pigeons, domestic fowls, and ducks all harbour these organisms and have been responsible for infection in man.[1] There are a number of closely related viruses, rather than a single strain; they are called viruses of the psittacosis-ornithosis group, which includes those causing psittacosis, acquired from contact with infected parrots, and ornithosis, which results from contact with pigeons[2] or other domestic birds. Man can be infected in various ways. The droppings of diseased birds and carriers contain the virus, which may be inhaled by people cleaning the cages or handling the birds. Bites by infected parrots may also convey the disease. Infection with viruses of this group is widespread in susceptible birds, but newly imported birds of the parrot family are a specially dangerous source of human infection.

In 1930, following a serious outbreak of psittacosis, with many deaths, a complete ban was imposed on the importing of parrots into this country. The ban was raised in December, 1951, and it is likely that a number of infected parrots have since been introduced. Indeed, the death on December 4, 1952, of the manager of a pets' corner in a department store was shown at the inquest at Birmingham to be caused by psittacosis acquired from infected parrots in a consignment of birds which he had received in November.

The onset of the disease is usually fairly acute and follows an incubation period of about 10 days. The symptoms are general malaise, severe headache, pains in the back and limbs, and sometimes nausea, vomiting, epistaxis, and photophobia. The patient is febrile, and often no other abnormal signs are found on physical examination. In a number of cases the condition remains a general febrile illness without localizing signs, and after lasting a few days the temperature falls and the patient recovers. In more severely ill patients evidence of pulmonary consolidation is found towards the end of the first week. Cough develops, but sputum is scanty or absent. The spleen is sometimes palpable. With suitable treatment the course of the illness can be shortened and the outlook greatly improved, but without modern chemotherapeutic agents the severe form of the disease carries a high mortality rate.

It is clear that there are no features of the illness

1 Bedson, S. P., *et al.*, *Virus and Rickettsial Diseases*. London: Edward Arnold. 1950.
2 Ellenbogen, B. K., and Miller, C. M., *British Medical Journal*, 1952, **2**, 189.
3 Report by the Virus Reference Laboratory, *Lancet*, 1953, **1**, 85.
4 Tasker, J. R., *British Medical Journal*, 1949, **2**, 362.

which point specifically to the diagnosis. Laboratory tests are of great interest and importance, but are not likely to provide immediate help. It is possible to isolate the virus from the patient's blood in the early days of the infection and from the sputum when lung involvement has occurred. A more generally applicable test is the demonstration of psittacosis antibody in the patient's serum. For this test two specimens of serum are required, one in the acute stage, ideally before the fifth day, and the second about the twenty-first day.[3] Although the finding of antibody in high titre (1 : 32 or over) in the first specimen is suggestive, a fourfold or greater rise in the second specimen is required for a firm diagnosis. At least 1 ml. of serum, preferably sterile and not haemolysed, is required for each specimen.

Psittacosis has been successfully treated with large doses of penicillin,[4] but the virus is more sensitive to the newer antibiotics. In view of the dangers of chloramphenicol, it would seem that aureomycin is the drug of choice, and if this is not tolerated terramycin, or large doses (2 million units or more a day) of penicillin, may be used. Because of the impossibility of diagnosing the disease early, it seems reasonable to regard as possibly psittacosis any illness starting acutely and being either influenzal in type or apparently a virus pneumonia in a person who has been exposed to ill birds of any species, and in particular recently imported parrots. Suitable treatment should be begun at once and the first of the two serum specimens taken. Specimens may be sent for investigation to the laboratories of the Public Health Laboratory Service in Cambridge, Cardiff, Exeter, Hull, London, Manchester, Newcastle, Northampton, and Nottingham.

ANGIOSPERMS AGAINST VIRUSES

The isolation of a substance from the seeds of the Norway maple which has an action against phage and vaccinia virus has recently been announced by Fischer.[1] The seeds were boiled with alcohol and ether, and the ground residue was extracted with dilute alkali, neutralized, and purified further by various procedures. The extract inactivated *in vitro* a phage of *Bacterium coli*, so that no phage multiplication took place when the host organism was added subsequently; the bacteria themselves were not affected by concentrations which were sufficient to inactivate the phage. Fischer also claimed that the extract inactivated phage after it had entered the host cell, but the evidence in support of this is open to question. The extract was not active against a staphylococcus phage, but inactivated vaccinia virus *in vitro*. The active principle in the extract was named acerin. The work reported is in no way unusual, and no exceptional claims are made for acerin by the author, who is rightly concerned to give a bare account of his findings. Observations of a similar nature are commonly made in virus laboratories all over the world.

It cannot be emphasized too strongly that *in vitro* tests are useless for detecting potential antiviral agents. The agents which inactivate viruses *in vitro* are many and varied, and range from the common antiseptics on the one hand to such innocuous materials as lipids,[2] physiological saline, and even distilled water on the other. Moreover, those few antiviral agents which are known seem to be active *in vivo* but not *in vitro*, and would thus have escaped detection in tests of the latter type; for instance, benzaldehyde thiosemicarbazone confers significant protection to mice inoculated intracerebrally with vaccinia virus, but does not destroy the virus when incubated with it in the test-tube,[3] and the growth of influenza virus in tissue culture is inhibited by certain amino-acids which do not inactivate the virus *in vitro*.[4] The method of preparation of acerin suggests that it may be a pectin, and the antiviral action of pectins has been known for some time. Thus Green and Woolley found in 1947 that the growth of influenza virus in fertile eggs was inhibited by apple pectin,[5] yet this discovery has not led to any development of clinical importance. It may thus be concluded that acerin, even if active *in vitro*, does not afford any easy solution to the virus problem nor even an important clue to it.

What hope does acerin hold for the future? Control of vaccinia-variola probably lies in the development of a thiosemicarbazone with a somewhat greater antiviral activity and a much lower toxicity, but Fischer's work on acerin will nevertheless be of importance if it directs attention to the possibility of finding antiviral agents in the angiosperms (that is, the flowering plants other than conifers). The storage organs of the flowering plants contain many compounds of a complexity such as to render them inaccessible by the methods of organic synthesis, and it might well be that some of these compounds might have by chance some activity, as for example against viruses, other than that which they exert naturally.

The Norway maple (*Acer platanoides*) is commonly used in this country for park and street planting, and the purple-leaved var. *Schwedleri* is a familiar object in suburban gardens. Abundant crops of seed are borne every autumn and there is thus no scarcity of material for anyone who wishes to confirm Fischer's observations and extend them by *in vivo* tests. The field maple (*Acer campestre*) and sycamore (*Acer pseudoplatanus*) also provide material for examination. The scope of such an investigation is almost unlimited, since it could be extended to cover the commoner members of the British flora, and it might well afford a better chance of a discovery of major importance in the field of virus chemotherapy than the methods which are being pursued at present. Much labour is required to produce a new synthetic compound, and the substances produced by plants in the course of their metabolism can be extracted at the cost of far less effort. If the report on acerin does nothing more than arouse an interest in flowering plants as a source of potential antiviral agents, it will at least have justified the attention which it has attracted.

1 *Acta path. microbiol. scand.*, 1952, **31**, 433.
2 Casals, J., and Olitsky, P. K., *Science*, 1947, **106**, 267.
3 Thompson, R. L., *et al.*, *Proc. Soc. exp. Biol., N.Y.*, 1951, **78**, 11.
4 Eaton, M. D., *et al.*, ibid., 1951, **77**, 505.
5 Green, R. H., and Woolley, D. W., *J. exp. Med.*, 1947, **86**, 55.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

ANTENATAL CARE—I. CLINICAL EXAMINATION

BY

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The half-century has turned since Ballantyne, of Edinburgh, published his article—"A Plea for a Pre-Maternity Hospital"—containing the first suggestion of an antenatal clinic or hospital. During these fifty years opinion and practice have changed, in some instances swinging a full circle. Maternity care is now accepted in this country as part of the Health Service that must be provided by the State. In England and Wales in 1951 there were 695,446 births (679,497 live births and 15,949 stillbirths). The number of mothers (new outpatients) who attended antenatal clinics attached to hospitals was 413,805, and 256,931 attended local health authority clinics. The total attendances made by expectant mothers (new and old patients) during 1951 was 2,333,902 at hospital clinics, and 1,450,097 at local health authority clinics. These figures, kindly supplied by the Ministry of Health, serve to indicate the magnitude of the service required for these expectant mothers.

The most striking recent trend in antenatal care is the increasing emphasis that is being placed on function as distinct from structure. The mechanistic approach to the parturient woman is to be deplored: the woman must be taken as a whole; her psyche and soma are so interwoven that neither can be neglected, especially at this most critical time of her life. In view of the improved physique of women in this country the anatomy of the pelvis should not be given the overwhelming emphasis that it has had in the past. The emotional aspect of pregnancy and labour is as important as the physical, but it has been neglected by doctors and midwives.

History

In addition to obtaining the history of general illnesses, operations, and so forth, it is of value to know something of the psychological background of the woman and her own mother's obstetric history. One should always inquire whether the mother has had any virus infection, particularly rubella, during the first trimester of pregnancy. It has now been established that there is an added risk of congenital malformations (deaf mutism, cataract, heart disease) when a woman has been exposed to such infection in the very early weeks of pregnancy. Severe vomiting early in pregnancy should be noted, since this is sometimes followed by pre-eclamptic toxaemia in the later months.

In a multipara a full history must be taken of the previous pregnancies and labours, including the puerperium. The weight, health, and method of feeding the baby must also be noted.

Physical Examination

Auscultation of the heart should always be performed. In about 50% of women attending an antenatal clinic a soft murmur will be heard towards the end of pregnancy. This is due to organic disease in only about 1% of cases.

The blood pressure should be taken at every visit, before any physical examination and after the mother has rested and been engaged in conversation for a few minutes. The limit of normal blood pressure in pregnancy is usually taken as 140/90, but as the result of Professor F. J. Browne's researches at University College Hospital it has been suggested that this ceiling should be dropped to 120/80. He has shown that a rise of blood pressure above this level has been present early in pregnancy in about 65% of cases of pregnancy toxaemia. It is to be regarded as an early warning sign of a future toxaemia of pregnancy.

The urine should be tested for albumin at each visit; if this is found, a catheter specimen must be obtained, since the original specimen may have been contaminated by vaginal discharge. If albumin is present in the catheter specimen then the urine should be examined bacteriologically. It is usual to examine for sugar at the first visit, and in some clinics this is repeated at each subsequent visit.

The height and the rate of increase in weight can provide useful information. Recent studies at Aberdeen by Professor Dugald Baird and his co-workers have revealed a relationship between the stature of a woman and the shape of her pelvis. In some of the small women (under 5 ft. —152 cm.) there was evidence of pelvic flattening as shown by *x*-ray pelvimetry. In women of normal and adequate stature the pelvic brim was gynaecoid (round) or anthropoid (long oval). When growth was stunted as the result of poor nutrition the pelvis was small and contracted, either android or platypelloid. The tall women in the Aberdeen investigation had no difficulties in their first labour. It has long been known that in the absence of a hereditary factor the stature of individuals is a measure of the nutrition of a community. If a woman is under 5 ft. (152 cm.) in height a careful assessment of her pelvic capacity must be made. A survey in 1940 of 500 London women attending University College Obstetric Hospital revealed a significant tendency for those of shorter stature to have a flatter pelvis.

Regular weighing at each visit is becoming the practice in more and more clinics. In the United States considerable importance is attached to the control of weight as a means of reducing the incidence of toxaemia. This will be referred to in more detail in Part II.

A vaginal examination should be made in all primigravidae, but not at the first visit. It should be postponed till after the sixteenth week, when the risk of abortion has diminished. If an ovarian cyst or other tumour is detected at this time the hazard of removal is minimal. In multiparae who have had normal deliveries there is no need to assess the pelvic outlet.

Pelvimetry

External pelvic measurements as a means of diagnosing pelvic contraction no longer occupy the hallowed place they held two or more decades ago. Nowadays they are taken routinely by medical students and midwives, and serve more as an anatomical exercise than anything else. This does not apply, however, to a woman of small stature (under 5 ft.—152 cm.), since in her case external pelvic measurements when carefully estimated may be a guide to the size of her pelvis.

There is a fairly high correlation between the greatest *transverse diameter* of the pelvic inlet (5¼ in.—13.3 cm.), and the *intercristal diameter*, which can be measured clinically with callipers with a fair degree of accuracy. Thus this measurement is more reliable in predicting the corresponding internal measurement than is that of the external conjugate in predicting the internal conjugate measurement. The intercristal diameter is measured between the widest points on

the outer borders of the iliac crests, and the average is usually considered to be between 10 and 11 in. (25 and 28 cm.).

A male distribution of pubic hair and hirsuties does not seem to be related to a masculine type of pelvis. The architecture of a female pelvis indicating a masculine tendency is a relatively narrow brim, a narrow sacrosciatic notch, a highly curved sacrum, a small subpubic angle, and an unusual degree of convergence of the side walls, or funnelling, leading to a narrow outlet.

The Diagonal Conjugate.—The majority of clinicians agree that this is the most important of all internal measurements. It is a digital measurement taken from the mid-point of the sacral promontory to the subpubic angle and is of value in estimating the internal conjugate. When there is cephalo-pelvic disproportion, and it is necessary to obtain this measurement with accuracy, then an anaesthetic will be needed, since the resistance of the perineum in some primigravidae will make the sacral promontory inaccessible to the examining finger. In the normal pelvis the promontory cannot be reached, and if it cannot be felt at 4¾ in. (12 cm.) from the lower border of the symphysis then the pelvic brim is usually adequate. Half an inch (1.3 cm.) is subtracted from this measurement in order to estimate the length of the true conjugate (4¼ in.—11.4 cm.). When the angle of inclination of the plane of the brim is greater than usual the promontory will be difficult to "tip" even in the presence of brim contraction.

Pelvic Outlet.—Much can be learnt from a careful digital examination of the outlet. The perineum should be palpated to ascertain its length and rigidity. With two fingers in the vagina the ischial spines, sacrospinous ligaments, lower end of the sacrum, and the subpubic angle can all be examined. The "knuckle" test (intertuberal) is familiar to all, but the measurement across one's own knuckles must be known. A rough estimate of the intertuberal diameter can be gained by pressing the clinched fist between the ischial tuberosities at the level of the anus. This intertuberal measurement is usually reckoned as 4¼ in. (11.4 cm.). If the subpubic angle is normal two fingers of average size can be placed within the pubic arch under the subpubic angle. With experience it is possible by these somewhat crude digital methods to detect the type of pelvic outlet that may give rise to difficult delivery.

X-ray Pelvimetry.—Routine radiographic pelvimetry of every primigravida is to be deprecated. There are enthusiasts who would like every pregnant woman to have her pelvis measured with radiological precision. They forget the expense incurred, the time consumed, the fallacies, and, last but not least, the danger with repeated exposures of radiation damage to the foetal gonads. Radiological methods should be used to supplement—not displace—the clinical examination, and *x*-ray pelvimetry should be considered only in the following clinical categories: (1) primigravidae with a height of 5 ft. (152 cm.) or less; (2) primigravidae with the foetal head not engaged at term and with variation in the anatomy and capacity of the bony pelvis as detected by digital examination; (3) primigravidae with a breech presentation in which external version has failed; and (4) multiparae with a bad obstetric history.

Dental Examination.—It is not sufficient for the doctor or midwife to make a perfunctory examination of the teeth and gums. The mother should be under the care of a dental surgeon as early as possible in pregnancy. He will advise on oral hygiene, further visits, and treatment.

Routine Chest Radiography.—Since 1947 every mother attending the antenatal clinic at University College Obstetric Hospital has had a radiological examination of her chest. The incidence of pulmonary tuberculosis detected early in pregnancy in this way has been about 1 in 200. All these patients had had the usual chest examination by the medical officer and in only one out of 27 were any abnormal signs discovered by this physical examination. Routine chest radiography of pregnant women should be obligatory, and, where it is available, miniature radiography might well be used for this purpose.

Preparation for Lactation

The clinical studies of Dr. Harold Waller at the British Hospital for Mothers at Woolwich have been a major contribution to this subject. He has shown that a defect can be found in one or both nipples in about 40% of women in their first pregnancy. Inspection is not enough, and he has devised a simple test which will reveal tethering of the nipple. Such fixation of the nipple interferes with suckling. Waller's test consists in placing the forefinger just above and the thumb just below the nipple's base at its junction with the areola. The finger and thumb are then pushed a short distance into the breast and squeezed together in imitation of the baby's bite. If the nipple retracts then the baby will have difficulty in feeding.

When this defect is present Waller recommends the use of a shield or "shell" made of glass or plastic.* The nipple projects through the hole in its base and the apparatus is kept in position by a well-fitting brassière. At first it is worn for a few hours daily and then throughout the day. It can be applied from the twentieth week onwards.

Waller has also shown how daily expression of the colostrum during the last eight weeks of pregnancy helps to eliminate lactation difficulties. All primigravidae and all who have had difficulty or have failed in previous lactation should be given prenatal tuition. Attempts to "harden" the nipple are to be condemned.

Special Examinations

As early as possible in pregnancy a sample of blood should be taken and sent to a laboratory for A B O blood-grouping, and Wassermann (Kahn) and Rhesus-factor testing. The haemoglobin should be estimated at the same time and again at the thirty-fourth week.

The simple haemoglobin test may lead to the detection of one of the more serious anaemias of pregnancy.

What is the lower limit of normal for the haemoglobin level during pregnancy? This is a controversial question, since there is a progressive increase in blood volume as pregnancy advances. The dilution of the circulating blood reaches a maximum of about 25% early in the last trimester of pregnancy. This physiological hydraemia results in a fall in the red-cell count and thus in the haemoglobin concentration. In a young woman during the last month of pregnancy 80% haemoglobin may be taken as the lower limit of normal; in an older woman (over 30) this figure is lower, about 76%. With increasing parity the haemoglobin level drops.

For many years the Tallqvist method of estimating haemoglobin has been used by general practitioners. Recently it has been criticized because of its unreliability. It is a useful procedure for the approximate estimation of haemoglobin. Although seemingly a somewhat crude procedure, the Tallqvist method has yielded results which are of about the same accuracy as those obtainable with most dilution haemoglobinometers, such as the Haldane and Sahli.

Frequency of Examination

It is usual to see the mother at monthly intervals until the thirty-second week, then again at the thirty-fourth and thirty-sixth weeks, and then weekly until the delivery. It is quite unnecessary to do an abdominal palpation at every visit. Provided there are no untoward symptoms, this examination should be done at the twenty-eighth, thirty-second, thirty-fourth, and thirty-sixth weeks. If the head is well engaged at the thirty-sixth week there is no need to do another abdominal palpation until term. The urine and blood pressure must be examined and the mother weighed at every visit. There is no doubt that many mothers are subjected to much purposeless palpation during antenatal supervision.

[*Part II will appear in our next issue.*]

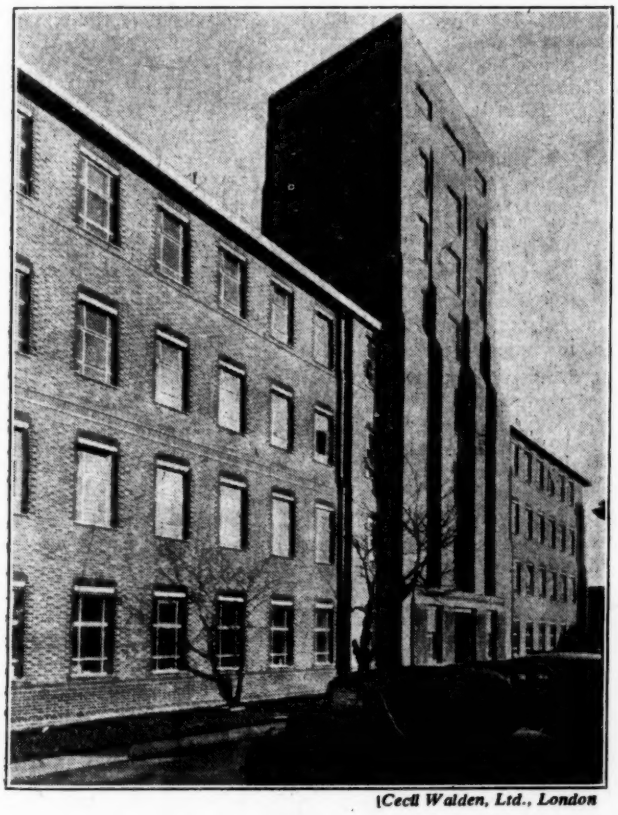
*Distributors are Allen and Hanburys Ltd., London.

CENTRAL PUBLIC HEALTH LABORATORY

MINISTER OPENS NEW BLOCK

The Minister of Health, Mr. Iain Macleod, opened a new block of laboratories at the Central Public Health Laboratory, Colindale, on January 15. Mr. Macleod, who was introduced by Lord Limerick, Chairman of the Medical Research Council, paid a tribute to all who worked in the Public Health Laboratory Service.

He recalled that, before the war, there had been a very haphazard service in this field. It had needed the whip and spur of war to start the story, another page of which was turned on this occasion. It was on the recommendation of the Committee of Imperial Defence that an emergency public health service had been set up. Although fears of bacteriological warfare and widespread epidemics were falsified, it had been realized that in peace as well as in war there was an essential need for such a service. It was a strange, casual, but very English way of meeting a great need in the ordinary life of the country.



[Cecil Walden, Ltd., London

Mr. Macleod spent an hour inspecting the building and learning about the work which was being carried out. He said that he was most interested to see the various reference laboratories. Some were main centres not only for this country but for Europe, the Commonwealth, and even the world—for example, the Enteric Reference Laboratory. "It is in such places as this," continued the Minister, "that the weapons against disease are to a large extent fashioned and sharpened. It is strange, when so many new diseases which used to be the scourge of this and other countries have yielded their secrets, there are still diseases like the common cold which defy us."

"A Microbiological Palace"

Colonel H. J. Bensted, Director of the Central Laboratory, said that the service had first been established, seven years ago, on the upper floor of a small Edwardian building. Later it extended to the lower floor, but even so its cramped conditions for working contrasted remarkably with the present "microbiological palace."

The new building has been completed in two years. It has enabled all departments to expand considerably, including those which remain in the old building (occupied before 1946 by the Government Lymph Department). Each floor is provided with sterilizing and wash-up kitchens, preparation rooms, and hot and cold rooms. There are special experimental rooms for the investigation of air-hygiene problems, and there are facilities for sterilizing the air intake of some of the rooms and the air exhaust from others where it may be contaminated by pathogenic bacteria or viruses. One entire floor is devoted to the study of virus diseases. This includes a special low-temperature suite consisting of chambers at 4° C., −30° C., and −70° C.

The following reference laboratories and special departments are contained in the new block and other buildings: the Standards Laboratory for Serological Reagents and the National Collection of Type Cultures (originally established as M.R.C. units many years ago); the Central Enteric Reference Laboratory; the Virus Reference Laboratory; the Salmonella Reference Laboratory; the Food Hygiene Laboratory; the Streptococcal and Staphylococcal Reference Laboratory; the Air Hygiene Laboratory; the Dysentery Reference Laboratory; the Epidemiological Research Laboratory; the Routine Department.

THE TECHNIQUE OF MEDICAL TEACHING

Another highly successful Conference-Course on the Technique of Medical Teaching was held at the Postgraduate Medical School, Hammersmith Hospital, London, on January 9 and 10. At the first session, presided over by the Dean of the School, Dr. C. E. NEWMAN, methods of group teaching were discussed in contrast to the formal lecture.

Group Teaching

Dr. L. J. H. BURTON, medical adviser to the Central Council for Health Education, offered some criticisms of the formal lecture. Sir William Hamilton Fyfe had said, for instance, "The lecture system has survived because it is cheap and easy. The stimulating effect of the lecturer fades away as soon as the lecture is over." And Sir John Simon, 75 years ago, declared that education was not something which one man could receive passively from another, but something which his own nature must grow forth most actively to meet. Dr. Burton pictured the lecture-theatre situation—the 40 minutes' lecture delivered behind the barrier of a rostrum, the front seats of the theatre empty and the back seats occupied by some whose interest was obviously in other things. In contrast with this was the discussion around the table, with its exchange of experiences and information and with each person in the group thinking actively in order that he should not disappoint the others.

Group discussion was partly interpretative and partly informative. It ensured that facts and opinions were scrutinized from many different points of view. Each student could fit his information into his own particular frame of reference. Everybody learned in a different way, and unless a teacher saw a problem in two or three different ways he would miss at least nine-tenths of the audience. Referring to the technique of group leadership, Dr. Burton said it would generally be found that questions which started with "How?" "Why?" or "What?" stimulated more useful discussion than vague questions which began with "Do you think?" The leader's main concern was to encourage all members of the group to participate and avoid the discussion being dominated by one aspect or one personality.

Miss M. L. JOHNSON, of the department of anatomy, University College, London, added some further observations on the value of group discussion. In practice, students selected from the lecture just what they could assimilate or what would fit in with the ideas they already possessed. In the discussion group, on the other hand, students were continually comparing and contrasting views, and examining the facts in their various relations. At a former conference the need to train students to treat patients as anxious and frightened people had been stressed. She thought that teachers should assume also that students are anxious, frightened people, and this was one of the golden rules of teaching.

At a later session, with Professor JOHN MCMICHAEL in the chair, a number of practical demonstrations were given of class teaching. The students taken were in their first, second, or third clinical years, and the teachers were for the most part junior teachers or senior registrars. However, from a conference point of view the result was not wholly successful, because the replies and observations of the students were in almost every case inaudible.

The Overburdened Curriculum

Professor G. PAYLING WRIGHT spoke of the growing size of the medical curriculum, and the need to relieve the burden on the student. Not all students of medicine ought to be forced into the same Procrustean bed. Medical education should be on less rigid lines than at present and try to adapt itself to providing the best fits for the widening variety of professional activities now available to young qualified people. At present, all medical students went through the same formal course irrespective of the branch of medicine in which they would ultimately be engaged. He believed that it would be possible to hold examinations in the preclinical subjects of anatomy, physiology, and biochemistry at two levels, one requiring a general and the other a more advanced knowledge. Every student should take all at the general and one, of his own choice, at the higher level. The load would be lightened and the educative value of the course improved. He thought it unsound psychologically so to arrange the course in some universities that students fatigued by the heavy strain of the second M.B. examination were precipitated after a wholly inadequate vacation into the "bridge term" of pathology and introductory clinical studies. As a result, many students failed to benefit as much as they should from this critically important few months of their training.

In the first clinical year the student had to absorb an enormous array of new facts, and much help could be given him by systematic didactic lectures. But during the remaining years, not only the subject-matter but the manner of its presentation should undergo evolution. With the increasing maturity of the student, the didactic lectures should be superseded by others of a less systematic and more stimulating kind. The aim of the educator should be to encourage mental independence in the student—to replace his natural desire to be "taught" by a capacity to "learn." He recommended that more attention should be directed to helping students to make use of libraries, because after leaving his medical school the reading of periodicals and monographs would be the main means by which a young doctor could improve his professional powers. The student should be introduced to the *Index Medicus* and the *Surgeon General's Catalogue*, and encouraged to use them to amplify his knowledge on interesting cases. Professor Payling Wright also suggested that some simple weekly or fortnightly "journal club," covering a few of the more important medical journals, and led perhaps by a registrar, might help the more senior students to bridge the difficult gap between textbooks and periodicals. Such discussions would ensure the active participation of the better students and train them to the critical appreciation of new advances in medicine.

The Museum in Teaching

Dr. KEITH SIMPSON said that many museums in medical schools and elsewhere had a constant and unchanging character; they were in the worst sense of the term "museums," often lacking reasonable comfort and adequate lighting. The museum at Guy's, of which he was curator, was a very large one, with about 8,000 specimens, but the size of a museum need have no bearing on its general practicability. Dr. Simpson showed examples of many ways in which the teaching facilities of a museum might be furthered, such as the use of photography, or of an artist, or by collating different stages in a condition or process, and by special methods of mounting. Specimens of use to elementary students on the one hand and to advanced students on the other could be marked accordingly, or collected into groups, and the artist could help to co-ordinate the clinical and pathological teaching in the museum by means of diagrams and cartoons. Lecture demonstrations on recent additions might be given as well as routine courses in medical or surgical pathology. No museum should ever appear to the student as an archaic, out-of-date collection of material, but as something abreast of the times and bearing upon the study which the student was making in other departments of the hospital.

Research and the Queue for Security

The last session of the course, with Professor IAN AIRD in the chair, was devoted to the question of how to introduce students to research.

Professor MAX ROSENHEIM stressed the value of research in producing a critical outlook in medicine, and discussed how students might be made more aware of the research in progress in their schools. He said that one of the principal dangers in medical practice to-day was the development of a stereotyped pathway to consultant posts. In America a period spent on investigation was regarded as an essential part of the training of the consultant, but in this country it was possible and even usual for a man to spend five or six years as registrar and senior registrar entirely at the bedside and in the out-patient clinic. Facilities for research existed, but were not fully used. There was lack of encouragement from above, and the young registrar was beset by the fear of turning away from the recognized pathway lest he lose his place in the queue for security. In his opinion every registrar should be given a research problem, however simple, and it should be possible for him to spend a period in a clinical or preclinical laboratory. It must, however, be made clear from the start, whenever a registrar was seconded for research purposes, that if eventually he found himself unsuited for a research career his time would not have been wasted. He should be able to return to clinical medicine not frustrated but enlightened and stimulated by his experience.

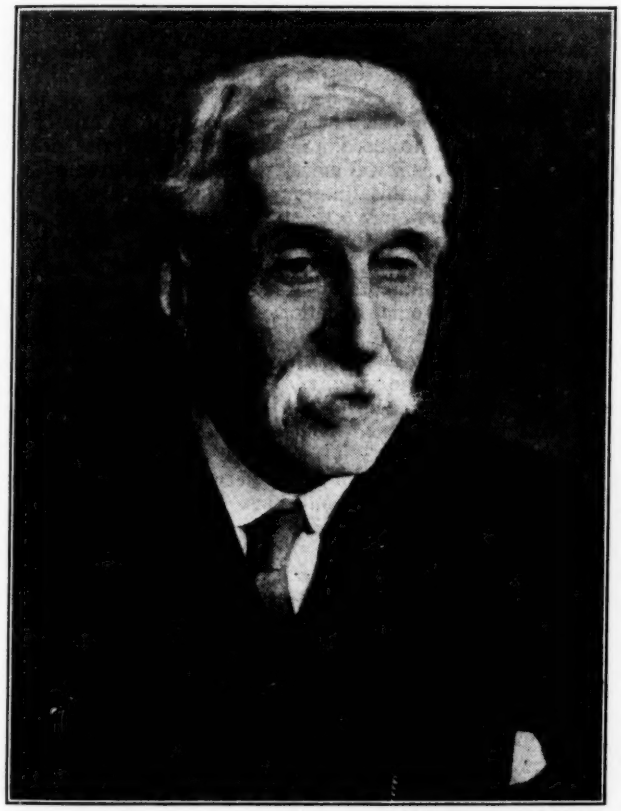
SIR LEONARD ROGERS, F.R.S., AT 85

The good wishes of many friends will have gone out to Sir Leonard Rogers on Sunday last, when he celebrated his eighty-fifth birthday. When he left India in 1921 after 28 years' service in that country the *Indian Medical Gazette* described him as "a prince of science." But the word "prince" suggests ease and glamour, which have been far from Sir Leonard Rogers's experience. No man has laboured more unremittingly, pursued research with a more ardent and inquisitive mind, braved with more unconcern the discomforts of climate and the occasional perils of the jungle or the laboratory. His energy and initiative have been unabated, whether in tracking down the causes of tropical disease to their lair or enlisting the help of business and official people in the beneficent projects he had at

heart. His work as professor of pathology at the Medical College, Calcutta, laid India and the East under his debt.

Those who know anything of the history of tropical medicine since the last decade of the nineteenth century will not need to be reminded of Sir Leonard Rogers's great work on amoebiasis and the placing of emetine treatment on a scientific basis; on cholera, with the working out of treatment by intravenous hypertonic saline; on the investigation of epidemic kala-azar in Assam and the application of antimony treatment; on the pathogenesis of sprue; above all on leprosy, whereby both the standard of treatment of that disease and the social lot of the leper have been extraordinarily improved.

When he came back from India he was still at the zenith of his powers. His labours, begun in Calcutta, were continued in London with equal zest. As physician to the Hospital for Tropical Diseases, as medical officer and afterwards president of the Medical Board of India, as founder of the British Empire Leprosy Relief Association, as author of a continual stream of papers and books on tropical diseases, as a vigorous fighter in the cause of freedom for research, his second career has been as strenuous as his first. Many of the present generation will have heard his occasional addresses to the Royal Society of Tropical Medicine or the Research Defence Society, but his work now goes back for 60 years.



[*Walter Stoneman, London*

When, a year or two ago, he published his autobiography, dedicated to his wife, "the best and most unselfish of women," he gave it the title of *Happy Toil*. The secret of the happiness was to be found, not principally in the engrossing nature of his researches, but in the religious faith which has sustained him through many difficulties and disappointments in accomplishing something for the relief of suffering. His work has gone on into old age: the publication in this *Journal* a few weeks ago of a contribution from his pen on progress in the control of cholera in India shows that he is as eager as ever to promote the welfare of mankind.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

"There is No Pathology"

SIR,—When a suspect organ or tissue is found to be normal reports about it sometimes state: "There is no pathology." Recently a candidate in an answer to a question in an examination paper stated that "one cause of torticollis was spinal pathology." There is an increasing use of the word pathology (which the *Oxford Dictionary* defines as "the science of diseases") when lesion or disease is meant. I would ask the courtesy of your columns to make a plea for the correct use of the word.—I am, etc.,

Cardiff. LAMBERT ROGERS.

Elliptocytosis

SIR,—May I ask, through the courtesy of your columns, that any pathologist who finds a case of elliptocytosis should be kind enough to let me know? A family has been found in which the gene determining this anomaly is on the same chromosome as the genes of the Rh blood group system (Goodall *et al., Ann. Eugen. (Camb.)*, 1953, in press). I am therefore anxious to do blood typing in some more families showing the same anomaly.—I am, etc.,

Galton Laboratory,
University College,
London, W.C.1. SYLVIA D. LAWLER.

The Climacteric and Oestrogen Therapy

SIR,—Your timely annotation, "The Climacteric and Oestrogen Therapy" (January 3, p. 37), will have encouraged many gynaecologists who are so often presented with problems associated with the menopause. Too frequently we see cases where indiscriminate use of preparations containing oestrogens, or a combination of hormones, has been made, and even more often cases of irregular and post-menopausal bleeding are sent to out-patient clinics without any information from the family doctor about previous hormone treatment. Close questioning may reveal that "pink pills" have been taken for some months "off and on," but apparently the patient has not realized for what periods of time they should have been taken. These things, as you have so wisely said, should not be.

I rather suspect, Sir, that I am not alone in regretting that all synthetic preparations of oestrogens are not subject to the Poisons Schedule; such a measure of control might discourage the casual use of these potentially dangerous remedies. Used properly and intelligently, these remedies can, as we know, be of immense benefit to suffering women (and men). But there is far too much careless and, in my view, dangerous prescribing of these things, and it is time indeed that the association of prolonged trickle-dosage with oestrogens and carcinoma in women of menopausal age should be recognized as a real danger.

Your article touches on the use of combined oestrogen–androgen therapy. It is true that extravagant claims have been unwisely made for such preparations, but I should like to put forward the suggestion that this combination may well be given a more extended trial in the suppression of unwanted lactation. Our experience in the Bath hospitals is that it is superior in action to testosterone; we long ago gave up the use of oestrogens alone for this purpose chiefly on account of their undesirable side-reactions.—I am, etc.,

Bath. A. LEECH-WILKINSON.

SIR,—In your annotation on "The Climacteric and Oestrogen Therapy" (January 3, p. 37) you rightly object to the indiscriminate use of oestrogen in menopausal disturb-

ances. It is amazing how many women throughout the world are receiving for relatively insignificant symptoms treatment with these substances which are experimentally carcinogenic. In view of the numbers at risk it is possibly misleading to assume that the experimental evidence does not apply to the human, and in fact I could describe cases where oestrogens given for long periods caused uterine cancer.

However much one can agree on this point with the author of your annotation, especially if oestrogens are administered by the entirely unnecessary method of injection or implantation, I object equally strongly to the statement that the combined use of oestrogen and androgen is pernicious because of the undesirable side-effects of both—namely, vaginal bleeding by oestrogens, and marked hirsutism by androgens. There is no doubt that many preparations of mixed oestrogens and androgens—and I have tested many of those sold here and on the Continent and in America—are so ill-balanced in their male and female hormone contents that these undesirable effects do occur and the result is worse than with oestrogen alone. A few of them, however, are far superior to oestrogen therapy alone. Since 1947 I have experimented with mixtures of female and male hormones and have published my results (International Congress of Gynaecology, Paris, 1951), "The Rejuvenating and Curative Effect of a Combined Androgen-Estrogen Tablet in Menopausal and Ageing Women and in Other Gynaecological Ailments, and a Hypothesis of Cancer Formation" (*Gynéc. prat.*, 1951, **2**, 213). I have never seen vaginal bleeding in cases so treated, and other authoritative gynaecologists—Greenhill, Greenblatt, Glass, Benjamin, and Margolies in America, de Watteville and Wenner in Switzerland—have had the same experience and are in favour of mixed hormone therapy. Slight hirsutism results in a few cases—in my experience up to 8%—presumably in those cases with a tendency to it. I have not met hoarseness, and, if the dose is kept to not more than two tablets daily for three weeks at a time, well-balanced preparations of ethinyloestradiol and methyltestosterone do not produce the undesirable side-effects described by the author of your annotation, even when the treatment is given over years.

If the author of this annotation would take the trouble, as I have done for years, to examine the vaginal cytology and the excretion of oestrogens and androgens before and after such treatment, he will certainly find that in many cases suitable amounts of androgen will counterbalance the undesirable effects of oestrogens, even in women who still have regular periods. The proper mixtures of these hormones not only give relief from the physical symptoms of the menopause but also act beneficially on menopausal depressions and other psychological symptoms in women who still menstruate and are troubled by premenstrual tension. I have sometimes observed in cases of sterility restoration of hormonal balance with subsequent pregnancy. As ageing women begin to elaborate less female and male hormones with resulting imbalance in their hormone metabolism, I can state emphatically that treatment with a female–male hormone mixture is greatly superior to the use of oestrogens alone if given in the correct dosage and the proper proportion, not to speak of the anti-carcinogenic effect of male hormone.—I am, etc.,

London, W.1. A. A. LOESER.

The Surgery of Varicose Veins

SIR,—Mr. R. Rowden Foote has mistaken my meaning (November 29, 1952, p. 1204) in his letter (December 20, 1952, p. 1359). I have never used any other than the avulsion or extraction method since 1915. As well illustrated in Mr. Foote's book, the operation is performed with the limb in the low or slight Trendelenburg position, so as to limit the bleeding. The vein comes away on the shank of the instrument pleated up (humped up or concertina-ed) with several short lengths of all the tributaries. The method is different from either the inside out (inverted vein withdrawal of Keller) or the ring-stripper method of Mayo, formerly called enucleation. Perhaps all this is just a matter of nomenclature, but it evidently needs clarifying. I may have unintentionally misled Mr. Foote when I wrote, ". . . Why [the authors] do not just extract the veins when the Babcock's extractor probe (not his original vein-stripper) has been positioned." When the vein and its tributaries are gone there is no further need of immediate local treatment other than removal of the blood and compression.

I have had no experience of a phenol sclerosant except perivenously. I imagine the sclerosing action is due also to the other hygroscopic ingredients such as glycerin and glucose which are usually in the formula. If so there must be some degree of delayed pain or sensation rendering them guidable in the way I have described (*British Medical Journal*, 1929, **2**, 848). This method is highly efficient, greatly reduces the number of injections, and lengthens the intervals between them.—I am, etc.,

London, W.1. G. H. COLT.

The Catheter and the Prostate

SIR,—I hesitate to cross swords with Mr. R. Marcus (December 27, 1952, p. 1414) on a bacteriological problem, but I feel that there are certain surgical aspects of the cases quoted by him which he has overlooked. In Case 1 a catheter was used to decompress a chronically distended bladder. As soon as it was empty the catheter was removed. Retention occurred, this time complete. What else could have been expected? Worse still, an ascending infection developed. Again, was this surprising? Since catheterization carries the risk of infection, was it reasonable to multiply this risk a hundredfold by allowing the retention to recur? With chronic retention, drainage, once started, *must* be maintained. In Case 2 the story is very similar, though the cystoscopy performed seemed to have been quite superfluous, the diagnosis being obvious. Presumably the infection which was already present in this distended and obstructed bladder was flared up by the instrumentation. Case 3 is mentioned as proof that slow decompression does not prevent haemorrhage. But this patient did not die of haemorrhage but of infection and uraemia on the fifth day. Has Mr. Marcus seen the type of haemorrhage which sometimes follows abrupt emptying of the bladder in such a spate as to carry the patient off in 24 hours before even the most virulent infection could get under way?

Mr. Marcus, speaking of immediate prostatectomy, says, "It is agreed that infection follows this operation, but it usually does no harm, because the urinary obstruction is removed." Surely the urinary obstruction can be overcome by skilful catheterization as well as by prostatectomy, provided the catheter is adjusted and looked after as carefully before operation as after. It may be argued that a catheter is bound to pick up and carry infection unless it is passed retrograde fashion. This seems to me to be very doubtful. I have not carried out any research into the bacteriology of the anterior urethra, but I have noticed again and again how consistently abacterial an abacterial urethritis proves to be. Moreover, it seems that with retrograde catheterization infection sets in just as inevitably and just as quickly as with the ordinary method.

Mr. B. H. Page in his letter (p. 1415) remarks, "It has yet to be proved that the infection which develops during a period of catheter drainage is due to the introduction of organisms at the time the catheter is passed," I am in entire agreement with him over this. Is it not the presence of a foreign body in the urethra that does the real mischief? I would like to agree with him also in thinking that the difficulty can be overcome by using latex catheters. Unfortunately I am now treating a case of stricture following an exceptionally smooth prostatectomy, with the patient passing clear urine naturally on the fourth day. The catheter used was a Foley of small calibre made of latex.

That catheterization or instrumentation of the prostatic patient is better avoided when possible because of the risks entailed is beyond dispute. That the risks are affected one way or another by the presence or absence of the gland and not by the circumstances attending its removal

is hard to credit. Immediate prostatectomy has the advantage of reducing the period of catheterization to an absolute minimum. Its disadvantages in certain cases are obvious.

I see that Mr. Wilson Hey (January 10, p. 99) rounds off his prostatectomies with a radical cure for hernia or hydrocele, or an appendicectomy. One supposes that most of these hernias are direct. Were the appendices acute or subacute? I do quite a few herniorrhaphies myself, but I am so fidgety about them that I rarely do the bilaterals in one stage. Then Mr. Hey drains the bladder of the patient returning from overseas with a suprapubic needle. This is something new. And, "The catheter passed 'with the full ritual of asepsis in a well-equipped hospital ward' . . . is more dangerous than one passed with proper care in the meanest cottage in this country." Really, Mr. Hey.

I have indeed read Professor Wells's monograph. It answers many important questions, and it raises many others, but, as Professor Wells himself suggests (January 10, p. 100), it would be otiose to enter on them here. One question, however, arises directly from the correspondence. How is it that four out of five of Mr. Hey's patients leave hospital on the tenth day with sterile urine, while all Professor Wells's patients become grossly infected, and one in five of them alarmingly so? We must all join with Mr. Hey in congratulating Professor Wells on reducing the mortality of this tricky procedure to 2%, although not all of us will give the credit for this achievement to the "aseptic technique." Careful haemostasis with uninterrupted drainage, forced diuresis, and the use of antibiotics may play as big a part as "asepsis."—I am, etc.,

London, W.1. STEPHEN POWER.

SIR,—The fundamental issue raised by Mr. Stephen Power's letter (December 6, 1952, p. 1256) is whether or not it is dangerous, because of the possibility of introducing sepsis, to employ a urethral catheter as a preliminary measure on patients suffering from retention due to a prostatic obstruction. Those who believe this advocate "emergency" prostatectomy for acute retention and prostatectomy without preliminary drainage for chronic retention even when the kidney function is grossly damaged. Most urologists agree that an average fit patient can be subjected to immediate prostatectomy with safety, though I personally consider that he is the better for adequate preparation, in particular the correction of fluid balance, even though this necessitates the use of an indwelling catheter for a day or two. As a routine procedure for absolute retention, however, there is much to condemn the emergency operation, for it does not permit the detection and control of the cardiovascular, pulmonary, and diabetic lesions so commonly associated with this group of patients. Sixty-four (47.7%) of 134 prostatic obstructions on whom I personally operated in 1952 were 70 years and over, and included 14 octogenarians. I mention this as a reminder that coincidental extraurinary ailments of advanced years are commonplace problems which must be taken account of in addition to the risks of urinary infection.

The problem presented by the patient with chronic retention, with a consequent marked renal impairment as evidenced by thirst, nausea, secondary anaemia, a high blood urea, and no visible excretion on intravenous urography, is different. My friends Mr. Wilson Hey and Professor Charles Wells (January 10, pp. 99 and 100) advocate prostatectomy of these uraemic or near-uraemic patients without first attempting to improve the impaired kidney function by bladder drainage, because they maintain this involves the risk of superadded infection and septic pyelonephritis. It has, however, never to my knowledge been confirmed that the insertion of a catheter or urethral tube during operation from the bladder outwards precludes the possibility of introducing infection, nor can it be accepted that Mr. Wilson Hey's operation is an "aseptic prostatectomy," involving as it does the insertion of a finger in the rectum and leaving a large uncovered area of the bladder base and prostatic urethra which has been subjected to diathermy. Professor Wells is prepared if necessary to spend half an hour in securing adequate haemostasis by diathermy of these areas, yet Mr. Wilson Hey claims that "a sterile urine in four out of five cases" will follow this technique in ten days. Mr. Wilson Hey had an initial 66% mortality in his group IV patients with a blood urea of over 200 mg.%, and a 16% mortality in his group III patients with a blood urea between 80 and 200 mg.%. He reduced these rates to 14.3% and 6.2% respectively by employing the indwelling urethral catheter when the urine was purulent, the suprapubic catheter when it was aseptic, and using intensive antibiotic therapy.[1] He thus himself confirmed that, contrary to his initial teaching, pre-operative bladder drainage was of benefit to some.

I certainly believe that preliminary drainage by suprapubic catheter[2] offers the best chance of recovery and subsequent prostatectomy for those in the uraemic or near-uraemic state, while the others with less severe renal damage can, with advantage, have the bladder decompressed and drained by an indwelling urethral catheter under a chemo-antibiotic cover until clinical improvement, confirmed by a falling blood urea, permits of prostatectomy.

As mentioned by Mr. B. H. Page (December 27, 1952, p. 1414), relief of prostatic obstruction by perurethral resection, in spite of the limitations of this method, can be accomplished with a post-operative mortality that is less than that claimed by any advocate of immediate prostatectomy, though catheter drainage is the usual preliminary to this procedure in cases of retention and the operation itself is, of course, entirely conducted by urethral instrumentation. How is this compatible with the theory that the use of a catheter in the prostatic is a mortal danger?

Professor Wells should not take exception to the criticisms of his advocacy, for some of us consider that a general application of the principles he champions might prove a retrograde step rather than an advance in the treatment of prostatic obstruction, and the subject must therefore be freely discussed.—I am, etc.,

Glasgow. ARTHUR JACOBS.

REFERENCES

[1] *Proc. roy. Soc. Med.*, 1949, **42**, 987.
[2] Riches, E. W., *Lancet*, 1943, **2**, 128.

SIR,—Mr. B. H. Page (December 27, 1952, p. 1415) mentions an aspect of this subject of which I have not read any satisfactory explanation. If the catheter is such a dangerous instrument as is now suggested, surely perurethral resection would be an extremely hazardous operation applicable only to the very "good risk" case. In actual fact the opposite view is widely held and supported by enormous experience all over the world. Many urologists who normally favour an open operation use the perurethral method for "bad risk" cases. Many general surgeons operate on good-risk cases themselves and refer bad-risk cases to the urologist for perurethral resection. Despite this adverse selection of cases the mortality of perurethral resection remains very low indeed, and follow-up over many years shows that the functional result is well maintained.—I am, etc.,

Glasgow. T. L. CHAPMAN.

Keller's Arthroplasty for Hallux Valgus

SIR,—In his paper "Hallux Valgus and Rigidus Treated by Arthrodesis of the Metatarso-phalangeal Joint" (December 27, 1952, p. 1385) Mr. N. Ross Smith advocates this procedure in preference to the Keller's type of arthroplasty which . . . leaves a shortened and much weakened great toe." While agreeing that Keller's operation does interfere with the function of the great toe, nevertheless a high percentage of good results can be obtained—particularly in feet which have efficient function in the remaining toes.

The results of Keller's arthroplasty in 41 patients (67 feet) treated in the orthopaedic department at Aberdeen Infirmary and followed up in 1949, three to seven years after operation, are reported for comparison. The results were graded subjectively, and at examination specific inquiry was made of symptoms and disability at the operation site and elsewhere in the foot.

Pain in the region of the second and third metatarsal heads was the cause of symptoms in 20 cases (30%). There was no efficient action of the small toes in these cases, and dorsal dislocation of one or more toes was found in four feet.

Results

Grade	Subjective Function	No. of Feet	Percentage
4	No symptoms. No disability ..	44	66
3	Intermittent symptoms. No significant disability	18	27
2	Persistent symptoms. Occasional disability	4	6
1	Persistent symptoms. Constant disability	1	1

Analysis of Results

Grade	Cause of Symptoms	Feet
3	Tender operation scar in cold weather	1
	Pain in longitudinal arch or ankle	2
	Intermittent metatarsalgia	15
2	Persistent metatarsalgia	4
1	Severe metatarsalgia	1

Metatarsal bars had been provided in five cases, four of whom at examination were free of symptoms : these cases are, however, included in Grade 3.

In conclusion, Keller's arthroplasty can give a reasonable proportion of good results. When there is no efficient action of the small toes, some form of forefoot support should be prescribed post-operatively.—I am, etc.,

Oxford. G. P. MITCHELL.

Ageing Cartilage

SIR,—There is no doubt that purely chemical analysis of body tissues has yielded much valuable information. The paper contributed by Dr. B. F. Matthews (December 13, 1952, p. 1295) draws attention to the inconstancy of the collagen/chondroitin sulphate ratio in certain joint cartilages, and differences in the composition of the articular cartilage of different joints. From what is known of collagen gels, and in view of the unequal distribution of force, both muscular and gravitational, such differences may be expected and have also been shown to occur with advancing age and in degenerative processes of cartilage.

It should, however, be emphasized that the matrix of articular cartilage of at least the juvenile and middle-aged subject is a complex gel in which there is a coarse, but relatively uniform, network of fibre-protein which one may regard as the disperse phase. The continuous phase is water, and the physical properties of the cartilage matrix may be modified by changes in the relative amounts of all three major components—water, collagen, and ester mucopolysaccharide. There are also small amounts of other compounds in the gel, some non-ionic, which may also influence the response of the gel to physical factors such as pressure and friction. A simple illustration of the importance of the water component of the gel is the changes which take place in a thin slice of cartilage upon dehydration. Toughness and rigidity are markedly increased and there is the concomitant optical change from opacity to transparency. This modification implies reduction of the "pore size" of the protein network, and is associated with markedly increased molecular orientation as shown by the enhanced birefringence and bireflection.

It is therefore suggested that the application of chemical analytical methods to the separation and estimation of the solid components of the matrix gel may confuse the picture when taken alone, since an appreciation of the physical chemistry of protein gels indicates clearly that the characteristic behaviour of the gel is not only concerned with the type and number of molecules present but also with their mode of association—i.e., linkages by primary valence bonds, Van der Waals forces, or longer-range ionic forces. The physical features of any gel substance and its *in vivo* function should therefore not be considered without due regard being given to the degree of hydration of the gel, as well as to the relative proportions of the two major organic constituents.—I am, etc.,

Bristol. C. H. G. PRICE.

The College of General Practitioners

SIR,—During the festive season our thoughts were wafting to the distinguished sponsors whose report adorned the front pages of the *Journal* of December 20, 1952, and firmly implanted the embryonic college in the history of British medicine. Nor do we forget, Sir, your words of blessing in the leading article (p. 1344). Among the college objectives the prestige of general practice takes precedence. Our president uttered auspicious words in his annual address: "The general practitioner should occupy a position second to none in the profession." But does the opening statement under "Conclusions"—"General practice is the oldest branch of medicine"—do justice to the noble cause that the college represents? May we more aptly conceive it as the parent of medicine—the "root and trunk" of the "tree of healing" with the specialties among its fruitful branches?

Conditions have changed in this half-century, and greatly to the disadvantage of the family doctor. The ethical core of medicine is the doctor–patient relationship. This intimate social bond has deteriorated gravely. Happily it is receiving signs of solicitude; but equally impeded is the mediatory function of the doctor in the extending specialist–patient relationship. The latter is causing dissatisfaction in the ranks of general practice, curbs the comity of the profession as a whole, and deserves a high place on the college agenda.

The profession falls into three groups: (*a*) general practitioners, (*b*) pre- and non-clinical laboratory staffs and research workers, and (*c*) specialists. The G.P.'s relations with group (*b*) are remote, affected little in the present issue, and need no more comment. It is regarding groups (*a*) and (*c*) that elucidation is urgently needed. Clear orientation of their relative positions is the first step in relieving the doctor of a grievous sense of lost terrain and caste. That he is too busy battling in the front line with the grim realities of human suffering to protest vehemently about his own degradation does not mean he lacks the sensibility of common humanity. Apparent indifference instead of vocal sympathy on the part of his colleagues makes him fret the more. But a manifestly intact professional camaraderie would confirm his determination to fight on until the good conditions in practice essential for decent professional work are won, and with them the final objective—prestige.

Encircling the layman nowadays is an assembly of diverse specialists with daunting polysyllabic titles. They are of two kinds, (*a*) "Harley Street," (*b*) "public health." Members of group (*a*) hold clinical positions, and it is to them the title of specialist ordinarily applies. Their variety has multiplied greatly owing to the advances of medical science. Group (*b*) embraces preventive medicine generally and includes those engaged at schools, factories, etc. Their notable increase is due to the urbanization of society. Humanity—already belonging to a general practitioner—now tends to congregate for its various occupations; there are often M.O.s attending who are engaged solely on specialist aspects of hygiene. Their contacts with patients are light and rather *ex officio*.

Despite the specialist's rather impersonal relationship his brilliant achievements capture public imagination, and the family doctor, who bears the major load of healing, is apt to lose in favour. In so many directions there have been encroachments on his province, although the most exacting parts of general practice remain his. Keenness suffers *pari passu* with loss of hold over his patients and increasing sense of detachment from his specialist brethren and hospital. The balance needs redress urgently—analogy points the way.

In his nuclear role the G.P. should be related to his specialist neighbour like a nucleus to nucleoli in the cell, and co-ordinate the team-work for the good of his patient. Someone must be captain, and, as he is primarily responsible for his patient's health, he is the obvious intermediary. He knows of each illness, the whole history, the personality and home background, and is honoured by the implicit trust of the patient. At the same time, aware of things from the consultant's angle, he must loyally represent his colleague's interest. Because society respects individuality and health is at stake, an adaptable service is vital. This ideal is attained by a harmoniously integrated group with the general practitioner pivotal. Judgment is constantly called for when dealing with suffering humanity—rigid regulations of commerce are out of place.

Why is the pre-eminence of the G.P. in the patient's purview indispensable? Because the patient who refers with assurance and confidence to "my doctor" is the most content; and the

doctor, conscious of such regard, is put on his mettle. *Per contra*, everybody's patient is nobody's patient. Again, the higher the esteem of the patient for his doctor, the earlier does he take his troubles to him and thence to the specialist, whose unceasing warning is, "The earlier the intervention the greater the chance of success." The patient, guided by his G.P., gets to the right specialist(s); unaided he would usually fail. From his viewpoint the young consultant needs to recognize that it is from the G.P. that there come the patients who add to his technical skill, the experience by which he rises to the top of his specialty and carries on the good work of riper years. Thus, in an evolving professional structure the G.P. remains on firm ground regarding status, and the debt due to him by his specialist colleagues is clearly manifest.

Prestige is a foremost topic in general practice to-day and of primary concern for the college, and is within as well as without the profession. Less dramatic as the domestic sphere may be, prudent reformers will first redress the lost balance there. Having consolidated their professional base, they will extend with unmitigated assurance on the wider public front.—I am, etc.,

Bristol, 8. A. WILFRID ADAMS.

SIR,—I am sure that I will not be alone in wishing to reply to the letter of Dr. Bernard Kendrick (January 10, p. 97), and would be grateful if you would accept a few observations on his diatribe. First, the college has been formed to satisfy the wishes and needs of a large body of general practitioners. Those, like Dr. Kendrick, who are self-sufficient in matters of clinical research and postgraduate education, and who do not feel that they have anything to offer or gain from their colleagues, will remain aloof. In other words, there are already a sufficient number of interested doctors to form the college and they have every right to do so, just as Dr. Kendrick has the right to remain an individualist and plough his furrow alone. The suggestion that "it is hoped to thrust upon us" such a college is quite erroneous. The college has in fact been formed by those interested, and the latter have no wish to thrust it upon anyone who prefers to remain without.

Dr. Kendrick calls for "a body of doctors who are persistent in helping to improve the medical service." What is the medical service if not the doctors who serve in it, together with their ancillary colleagues? If the aim is to improve themselves, how better could the general practitioners seek to improve the service as a whole? It is interesting to learn that principals do not need help in finding suitable assistants. I had always been under the impression that to sort and evaluate 50 applications for a post was a very difficult task when the applicants' previous experience might be to a large extent unsuitable for the type of practice in question and, in some cases, their interest superficial and pecuniary. If Dr. Kendrick wishes to devote his energies to "helping assistants to become principals"—a very laudable aim—the various medico-political organizations offer suitable channels, and in the meantime the College of General Practitioners will carry on with the work of giving them every opportunity, if they wish to accept it, of becoming good or even better principals.

As for the suggestion that the college may restrict entry into general practice, I am sure that the sponsors have never dreamed that such power might one day be theirs—and when that time comes I am sure that they will be content to allow the law of supply and demand to remain unaltered.—I am, etc.,

Sheffield. H. H. PILLING.

SIR,—With reference to the proposed College of General Practitioners, I would like to support Dr. A. G. Cruikshank (January 10, p. 98) in his proposal for membership examination. Membership is worthless while it can be obtained for 10 guineas and a promise to do three days' "refreshing" a year.

Twenty years' successful doctoring does not always presume a high standard. A large "successful" practice means little more than an ability to please the patient—and this is not by good doctoring in every case. Examinations, for all their defects, are the only practical way to assess one's knowledge. Let us combine, say, five years' general practice with an examination on the most general and practical lines—eliminating as far as possible theoretical questions.

As to functions of the college, not the least should be teaching and research. In general practice one often recognizes unrecorded epidemics, unrecorded because the cases never reach hospital; to mention a few—Bornholm disease, streptococcal infections, often followed by epidemics of fibrositis, herpes zoster, urticaria, and minor "influenzal" infection. Even cystitis seems to be epidemic at times. One of the faults of the present system is that each consultant has such a limited field of knowledge that he is unable to weigh up the importance of his own special findings in the picture of the patient as a whole. Who is to assess which is the most important factor in, say, a case of mitral stenosis, pregnancy, and anxiety neurosis? The college might encourage the emergence of a consultant general practitioner of wide knowledge, whose function would be to assess the importance of all the specialist findings.

We would then arrive at the position where the reflections on general practice would be replaced by, "Poor old Smith has failed his M.C.G.P. so he will probably have to specialize."—I am, etc.,

Dundee RONALD A. B. RORIE.

Emphysema

SIR,—The report of the erudite address by Dr. A. G. W. Whitfield (December 6, 1952, p. 1227) has raised some important issues. Dr. Whitfield refers to the use of morphine in patients with cardio-respiratory failure, and rightly asserts that its dangers are "well, but not sufficiently well, known." However, your correspondent Dr. W. N. Leak (December 27, 1952, p. 1416) appears to hold the view that morphine can sometimes be used with benefit in such cases. Unfortunately, he made no attempt to define the clinical criteria which would enable the practitioner to decide which of these cases could be given morphine with "safe and useful" results. On the contrary, there is a wealth of evidence to show that the use of morphine in cases of the asthma-emphysema complex, etc., is fraught with grave danger. This drug not only depresses the respiratory centre, but also inhibits the cough reflex. In the case of status asthmaticus the patient's very life depends on the untrammelled activity of these physiological mechanisms. Furthermore, morphine is an addicting drug which should not be given to those suffering from a chronic, painless malady. The fact that many patients survive an injection of morphine is no justification for its use, since others are less fortunate. The value of morphine in so-called cardiac asthma is, however, generally accepted.

The use of ephedrine is logical in cases of emphysema with *marked* bronchospasm. Nevertheless, I have seen the rapid onset of congestive heart failure immediately following the use of ephedrine in a case of cyanotic emphysema with minimal bronchospasm. The patient improved somewhat on withdrawal of the drug, and made further progress with its substitution by thiouracil. The increased metabolic rate produced by ephedrine may be dangerous to these precariously situated (cyanotic) patients.—I am, etc.,

Littlemore, Oxon. J. TODD.

Post-epileptic Automatism

SIR,—I am grateful to your correspondents who have expressed their views regarding post-epileptic automatism. It is significant that no one has produced any evidence to support the idea originally put forward by Mercier and repeated by Norwood East. This is that the automatism repeats some previous behaviour: the woman wringing out washing has a fit and wrings her child's neck, the man peeling potatoes cuts someone's throat, and so on. Such a theory is too good to be true and is obviously erroneous.

It would seem that post-epileptic behaviour can range from a simple reflex act such as passing urine to some complex behaviour which, as Dr. F. A. Pickworth says (December 27, 1952, p. 1414), may have been elaborated only in fantasy. It is time that the false view of Mercier was eliminated from the books on medical jurisprudence, and one hopes that when Sir Norwood East's excellent book goes into another edition he will rewrite this section.—I am, etc.,

London, W.1. CLIFFORD ALLEN.

Mind and the Skin

SIR,—I must apologize for taking up your valuable space with further discussion regarding my paper on "A Case of Congenital Ichthyosiform Erythrodermia of Brocq treated by Hypnosis" (August 23, 1952, p. 422), but several points in Dr. F. L. Lydon's letter (December 20, 1952, p. 1356) require clarifying.

When Dr. Lydon last saw the case it was at the meeting of the Royal Society of Medicine, and still undergoing treatment. The case was presented before treatment was completed to show the marked gradation of improvement in different areas, in complete accord with the length of time these areas had been treated by hypnosis—that is, the left arm almost clear, the right arm not quite so clear, and the legs where improvement was just beginning. If Dr. Lydon refers back to my paper he will see that this order of improvement was precisely that in which treatment was carried out. The reason for this somewhat devious method of treatment was so that there could be no question that hypnosis, and hypnosis alone, was responsible for the improvement. "If hypnosis was responsible for the reported improvement . . ." writes Dr. Lydon. If hypnosis was not responsible, I would be glad to learn what was. It was certainly not an ointment or potion; those had all been tried for years previously, to no avail.

Dr. Lydon writes that he was not impressed by the clinical improvement in the case; however, other observers do not agree with him. Drs. M. S. Thomson and D. I. Williams saw the case before its presentation at the Royal Society of Medicine and considered the improvement even then remarkable. In fact, it was at their suggestion that the case was shown to the Dermatological Section of the Royal Society of Medicine. Sir A. H. McIndoe and Mr. F. T. Moore endorsed their suggestion. Dr. F. R. Bettley wrote (November 1, 1952, p. 996): "I had the privilege of seeing the patient when Dr. Mason demonstrated him at the Royal Society of Medicine, and I think the general reaction, like my own, was of more than surprise; it was fantastic, but true." Drs. Sulzberger and Baer, whom Dr. Lydon quotes in support of his broadside against psychiatric workers, consider the case of sufficient interest to include it in their *Year Book of Dermatology and Syphilology* for 1953.

Dr. Lydon then goes on to say: "If hypnosis was responsible for the reported improvement it only needed a further period of treatment to bring about complete clearance of the lesions." I can see no necessity for this. There are many drugs and forms of therapy which cause improvement without total cure, and one cannot infer that a further dose of the drug or prolongation of the particular therapy must cure the disease. To say that if one dose improves then two or three must cure is to teach mathematics, not medicine. He continues: "Failure to record further improvement must of necessity cause a critical observer to discard hypnosis. . . ." To state that any form of therapy must either totally cure a disease or be discarded is to condemn most of medicine as it stands to-day. We should by these standards discard most of physiotherapy, the medical treatment of asthma, hypertension, nephritis, and peptic ulceration, E.C.T. and insulin in psychiatry, and calamine and ichthyol in dermatology. Palliation still remains our greatest function.

I would like to point out again to Dr. Lydon that this is a case of a congenital structural disorder affected by a psychological process, a fact which is extraordinary in itself. The change in the boy's skin remains the same to-day as it did when I first reported it over a year ago—that is, 70% of the total areas affected have been cleared; no further improvement has taken place and no regression of the cleared areas has occurred. That the condition is not totally cured is sad for the patient, but does not detract from the fact that a hitherto unsuspected factor in the pathogenesis of the disease has been brought to light. Dr. Lydon accuses us of lack of objectivity; I suggest he goes back and looks at the photographs of the case again—the camera at least is objective.—I am, etc.,

East Grinstead. A. A. MASON.

SIR,—In company with Dr. F. L. Lydon (December 20, 1952, p. 1356) I too have personal knowledge of Dr. Mason's case of congenital ichthyosiform erythrodermia of Brocq. When Dr. Lydon saw this case at the Royal Society of Medicine on March 15, 1951, the patient's left arm was completely clear, and the right arm almost so. It is therefore astonishing that Dr. Lydon was ". . . not so impressed by the clinical improvement in the patient's skin condition." When this case was under Dr. Lydon's care, both arms were thickly covered with hard, ichthyosiform scales. This remarkable change followed hypnotic suggestion alone. Dr. Lydon seems to throw some doubt on the foregoing when he queries whether "hypnosis was responsible for the reported improvement. . . ." The improvement was not only reported, he saw it with his own eyes at the R.S.M., and if he requires further proof he can be provided with a list of doctors who were witnesses to this fact, before, during, and after treatment.

Complete clearance of the lesions has not occurred to date, which is also mysterious, but in no way detracts from the partial relief obtained. Dr. Lydon does not seem to realize that the patient, a 16-year-old boy, was completely incapacitated by his disability before treatment by hypnosis. Not only were his hands useless, his skin unsightly and painful, but he was cut off from social contacts owing to the offensive smell emanating from the affected areas. At the risk of repeating information which has already appeared in this *Journal*, may I remind Dr Lydon that the patient's skin is now approximately 70% cleared, the foul odour has gone, and the young man is working for his living? He is not completely cured, but do doctors ever cure patients? If it were possible to observe them from birth to death, and be able to say at the end that we had eradicated the tendency to illness, then and then only could we speak of cures. Lacking these circumstances, the doctor can only relieve illness as it occurs, and he should be willing to examine and give trial to any method of treatment aimed at relieving his patient.

Dr. Lydon's choice of quotation from Dr. Sulzberger's paper[1] is an example of the danger of lifting remarks from their context. In the same paper Dr. Sulzberger states: "It may be necessary at this point to emphasize our full realization that it is an obvious error to think of any somatic disease or reaction as purely and exclusively somatic, or of any psychic disease as purely and exclusively psychic. Psyche and soma together form a single unit: they are so integrated, so inextricably dovetailed and correlated, that it is only in combination that they form the functioning organism. It is therefore probably not an exaggeration to state that no psychic change can possibly fail to exert some effects on the body and bodily functions, and that no bodily change can take place without some effects on the mind and the emotions." I had the opportunity of meeting Dr. Sulzberger at the Tenth International Congress of Dermatology in London last summer. He was sufficiently interested in the paper "The Value of Hypnosis in the Treatment of Skin Diseases" (Dr. Hugh Gordon and Dr. K. H. Cohen)[2] to come to St. George's Hospital, observe the use of hypnosis, and question several patients who had benefited from this treatment. As a result, he invited Dr. Mason and myself to the Skin and Cancer Unit at New York University for the purpose of demonstrating the method.

For several years I have been treating chronic skin patients—at first using classical dermatological procedures. I found, as so many dermatologists have before me, that one was left with a vast number of cases which did not improve or indeed grew worse. The decision was made to try using hypnosis and simple psychotherapy, and this treatment has been applied for the past eighteen months, with the result that 70% of previously resistant patients have been discharged. It seems that the patients who responded were not suffering from skin disorders *per se*, but their skin reaction was one factor among others in a disturbed emotional state. Recognition of the psychic factor in the

aetiology of skin conditions does not, as Dr. Lydon suggests, provide an "easy way out." On the contrary it is an arduous and exacting form of therapy, for one is called upon not only to relieve the condition but to counteract the by now fixed idea in the patient's mind that he is suffering from physical disease or is the victim of external noxious agents.

It is difficult, and perhaps unnecessary, to fit these patients into psychiatric classifications. In fact one of the outstanding features of psychosomatic disorders is the total failure of workers in this field to assign a particular disorder to a particular personality group. What is urgently required is relief of the patient's condition, and in order to achieve this the physician should be willing to listen to the patient's, and often immediate relations', stories, however irrelevant they may seem, for therein lies the guide to his treatment. The human spirit cannot be imprisoned in the confines of "the only truly scientific method of study—the objective approach." This way ignores the sufferer in the interests of impure knowledge.—I am, etc.,

London, S.W.1. KATHRYN H. COHEN.

REFERENCES

1 *Year Book of Dermatology and Syphilology*, p. 37, 1951, Chicago.
2 Excerpta Medica, 1952, 6, Sect. 13 (Dermat. and Venerol.), 361. Synopsis of paper.

*** This correspondence is now closed.—ED., *B.M.J.*

The Neurology of John Hunter's Last Illness

SIR,—I have read with interest the paper by Sir Russell Brain (December 27, 1952, p. 1371) and find a correlation of the symptom-pathology with that often seen in cases of mental disease. The episodic character of the vertigo, epilepsy, loss of memory, sensory hyperaesthesiae with irradiation, distortion of visual images, auditory pulsation, and diarrhoea, contrasts with the complete absence of gross lesions in the central nervous system and the constant presence of cardiovascular lesions. Similar absence of lesions of the neurone and presence of cardiac pathology has been noted by A. Batty Shaw[1] and other workers, who "suggest that the neurological disturbance may have been due to ischaemia and anoxia from fall in blood pressure, associated with narrowing of the cerebral arteries."[2] In my book[3] I illustrate a localized area of hyperaemia typifying reactive hyperaemia to a temporary occlusion of a cerebral arterial branch (Plate II, a). Such cortical hyperaemia is known to lower the resistances of the synapses, and would thus account for the hyperaesthesiae with irradiation, the epilepsy, and other symptoms depending upon the locality, of the ischaemia predetermined by the vascular pathology.—I am, etc.,

Birmingham. F. A. PICKWORTH.

REFERENCES

1 *Lancet*, 1952, 1, 763.
2 Ibid., 1952, 1, 652.
3 *New Outlook on Mental Diseases*, 1952. Bristol.

Christmas Disease

SIR,—We read with enjoyment the letters by Drs. D. H. Collins and P. R. Kemp (January 10, p. 97) and are glad that our name "Christmas disease" gave them a seasonal opportunity to enjoy themselves. In fact, since medical terminology abounds with names far more peculiar than Christmas, an extension of this variety of humour (with due care to avoid impropriety) could enliven your correspondence for weeks.

In compliance with the suggestion of Dr. Kemp, may we submit to you, Sir, for consideration the names we discussed before choosing Christmas disease, with brief reasons for their rejection? Aetiological terms are satisfactory only if the aetiology is clear, and attempts to devise one for Christmas disease led us into deep water. The factor missing in this condition is probably, but not certainly, a co-factor for a precursor of the precursor of thromboplastin and might thus be called "coprothromboplastinogen." Following established practice, the disease could then be termed "hereditary hypocoprothromboplastinogenaemia," but this would be subject to alteration should the factor be found later (as is very possible) to be, say, a co-factor for a co-factor of thromboplastin. What would Dr. Kemp feel about "hypococothromboplastinaemia"?

Terms like these could be avoided by continuing the practice of numbering the clotting factors. But these factors probably react in a sequence at present undetermined, and the numbering must be related to this sequence to be intelligible. We might call the factor under discussion "Factor 8" (or 9, or 10), but if it were later found that another is interposed between those already numbered 8 and 9 we should have to renumber or call the new factor "8A," or even "8½." In any case, would such a name as "Hereditary Blood Clotting Factor No. 8 Deficiency" be acceptable? The unassuming term "Christmas factor" has only been used temporarily, being admittedly unsatisfactory, though there is precedence for calling factors after the conditions produced by their deficiency (for example, "P.A. factor"). Following a suggestion by Dr. Robb-Smith, the name will probably be abbreviated to "X" or "χ," which should forestall any suggestion by your correspondents that its possible precursor should be known as Christmas Eve factor.

Failing the aetiological approach, another is to devise some name suggesting the symptomatology. Christmas disease resembles clinically the inaptly named condition haemophilia, and variants of this word were considered. But pseudohaemophilia, parahaemophilia, and haemophilia 1 and 2 have already been used. "Metahaemophilia" and "haemophilia B" were suggested, but it is actually desired to emphasize the distinction from, rather than the similarity to, haemophilia. Moreover, if Christmas disease becomes "haemophilia B," then haemophilia must be renamed "haemophilia A" and antihaemophilic globulin "antihaemophilic A globulin," with possible repercussions from the International Haemophilia (A?) Society. By a cautious approach to a classical scholar we might be able to produce some appropriate Graeco-Latin concoction, but angiostaxis, hemogenia, thromboasthenia, and constitutional thrombopathy are in use, and the number of clinically similar diseases awaiting differentiation will probably outrun classical invention.

Finally, coming to eponyms, modesty prevented us from referring to the condition as the "Biggs–Dacie–Douglas–Macfarlane–Merskey–O'Brien–Pitney syndrome," and, faced by the difficulties described, we felt that "Christmas disease" was a legitimate, unassuming, and pleasantly provocative term. After all, Dr. Collins asserts that thousands of your readers turned to our article because it was headed by this name. How many would have given it a glance had it been called, for example, "Hereditary Orthothrombophobia"?—We are, etc.,

ROSEMARY BIGGS.
A. S. DOUGLAS.
Oxford. R. G. MACFARLANE.

Acute Laryngotracheobronchitis

SIR,—I would like to apologize for the delay in replying to Dr. J. S. Taylor's letter (December 20, 1952, p. 1361), but both Dr. Heseltine and I are, at the moment, in Canada. It is true that a combination of penicillin and aureomycin was used in three cases. The reason why penicillin was given in early treatment has been described in the paper. In these cases only one dose of crystallized penicillin was given, and aureomycin was commenced as soon as the child could swallow.

Dr. Taylor is, of course, right when he assumes that penicillin and aureomycin could be antagonistic. A considerable body of work has now accumulated to prove this point, and Jawetz arranges the antibiotics in two groups: (1) Penicillin, streptomycin, bacitracin, neomycin; and (2) aureomycin, chloramphenicol, terramycin. He points out that members of group 1 are frequently synergistic, but never antagonistic. Members of group 2 are neither synergistic nor antagonistic, but when group 1 and group 2 are combined, depending on the susceptibility of the microorganism, antagonism may result. I have listed below some

of the more important references of Jawetz *et al.*[1 2 3] His work is confirmed by Lepper and Dowling,[4] who have shown definite antagonism between penicillin and aureomycin in the treatment of meningococcal meningitis.

Our patients who received mixed antibiotics were treated in this manner before we were aware of antagonism—that was in 1950. They only received one dose of crystalline penicillin, and I feel that it is unlikely to have caused a resistance, but this statement is made purely on impression.—I am, etc.,

Winnipeg, Manitoba. J. NIXON BRIGGS.

REFERENCES

[1] *Arch. intern. Med.*, 1951, **87**, 349.
[2] *Amer. J. med. Sci.*, 1951, **222**, 404.
[3] *Arch. intern. Med.*, 1952, **90**, 301.
[4] Ibid., 1951, **88**, 489.

Foetal and Neonatal Death

SIR,—The memorandum "Neonatal Death due to Ligation of Umbilical Cord by an Amniotic Band," by Drs. F. O'K. Craven and C. J. M. Geddes (January 10, p. 81), contains an unfortunate example of confused terminology.

The memorandum begins: "The following case of neonatal death is interesting enough to be placed on record. So far as we can ascertain no previous foetal death due to this exact cause has been published." This wording suggests that neonatal death and foetal death are the same thing, but this is not so. *Neonatal death* means death within the first 28 days after birth of a child that had been born alive, whereas *foetal death* means that the child had died before or during birth. It is important in many ways that this distinction be understood and maintained.

It is stated later in the memorandum that "a dead baby had . . . been delivered." This being so, the use of the term "neonatal death" is quite inappropriate in this case.—I am, etc.,

W. P. D. LOGAN,
Chief Medical Statistician,
General Register Office.

London, W.C.2.

POINTS FROM LETTERS

The College of General Practitioners

Dr. D. D. MACDONALD (London, N.1) writes: The College of General Practitioners has been launched and looks gay in the paint of good intention, rich in the promise of high performance. One watches with the interest of good will from the bank and hopes the correct solution will be available, in full measure, to resolve its problems to come. In wishing this great venture, this New Elizabethan vessel, all success in real usefulness, the words of Samuel Langhorne Clemens (Mark Twain) come welcome to mind: "Diligently train your ideals upwards and still upwards towards a summit where you will find your chiefest pleasure in conduct which, while contenting you, will be sure to confer benefits upon your neighbours and the community. This has been taught by all the great religions for ten thousand years. The only thing new about it is that this time it has been candidly stated. That has not been done before."

Dr. A. E. STEVENS (Jersey) writes: "The College and the Hall" (M.R.C.S., L.S.A.) were good enough for our medical forebears. To-day we have the Royal College of Physicians and the Royal College of Surgeons, which are surely sufficient seeing that so many of us derive our registration on the strength of their diplomas. The Royal College of "Accoucheurs" is quite redundant and unnecessary; and now there is a demand for a College of General Practitioners. If it has to be, why not indicate from its name that it is at least connected with medicine? Why not College of Medicine, or better still College of Apothecaries? But it should be borne in mind that such a college is tantamount to the acceptance of our lowered status.

Otitis and Ear Syringing

Dr. W. STANLEY SYKES (Morley, near Leeds) writes: Mr. A. Tumarkin (December 20, 1952, p. 1361) recommends that cases requiring ear syringing for wax should be sent to an E.N.T. specialist. Surely, Sir, there should be two groups of specialists for operations of this magnitude—one for the right ear and one for the left.

Obituary

F. E. SAXBY WILLIS, *M.C.*, M.D., M.R.C.P.

Dr. F. E. Saxby Willis, who died on January 2 in Hampstead General Hospital, had been the senior physician there for many years.

Frederick Edward Saxby Willis was born in London on October 21, 1889, the son of Frederick and Alice Willis, and received his early education at Dulwich College. He then entered St. Bartholomew's Hospital Medical College and qualified M.R.C.S., L.R.C.P. in 1913. On the outbreak of war in 1914 he enlisted in the South Staffordshire Regiment and was severely wounded at Ypres in 1915. On recovering from his wounds he entered the R.A.M.C. and was attached to the Seaforth Highlanders until the end of the war, being awarded the Military Cross in 1917 for attending to wounded under heavy fire. After demobilization he obtained the degrees of M.B., B.S. of the University of London in 1920 and became casualty physician and chief assistant in the children's department at St. Bartholomew's Hospital, a position he held for several years. In 1922 he proceeded M.D. and took the M.R.C.P. In due course he was elected to the honorary staff of the Royal Chest Hospital and the Hampstead General Hospital. Despite the handicap of his war wounds and, later, diabetes, he refused to allow them to interfere with his daily activities, and he built up a large consulting practice in lung diseases and general medicine. At the time of his death Dr. Saxby Willis was senior physician to Hampstead General Hospital and to the Royal Chest Hospital. He was also physician to the Weir Hospital and consulting physician to the Metropolitan Ear, Nose, and Throat Hospital, to Yateley Cottage Hospital, and to the Alexandra Orphanage.

With the advent of the National Health Service in 1948 he became a member of the teaching staff at the Royal Free Hospital School of Medicine and gave clinical lectures to students and postgraduates there. He contributed many papers on diseases of the lungs to the medical journals, and his joint contribution on cystic diseases of the lungs has been included in Davidson's *Practical Manual of Diseases of the Chest*. At the time of his death he was keenly engaged in a research survey of "atypical pneumonia" for the Royal Free Hospital School of Medicine, and it is to be regretted that his personal conclusions on the aetiology and clinical aspects of this syndrome will not be available to the profession.

Saxby Willis's sympathetic manner and genial personality endeared him to his many patients. His colleagues also had a deep affection for him, and, whether at hospital board meetings, clinical lectures, or social functions, he was the centre of attraction. He leaves a widow and two sons and two daughters, to whom we offer our deepest sympathy.—J. V. A.

B. L. JEAFFRESON, M.D., F.R.C.S., F.R.C.O.G.

Mr. B. L. Jeaffreson, well known in Leeds as a gynaecological and obstetric surgeon, died at his home at Leeds on January 7 at the age of 56.

Bryan Leslie Jeaffreson was born in London on August 29, 1896, the son of Mr. H. J. Jeaffreson. Several of his forebears, who came from Framlingham, in Suffolk, were eminent surgeons in their day. He was educated at Hurstpierpoint College, and at St. Bartholomew's

Hospital Medical School, which he entered in August, 1914. A year later, having passed the first M.B. examination of the University of London, he enlisted as a private in the Honourable Artillery Company and served as a combatant in France. In 1917 he was invalided out of the Army and returned to the study of medicine at St. Bartholomew's Hospital, graduating M.B., B.S. in 1921 and winning the Willett Medal for operative surgery in the same year. He held successively the posts of house-surgeon and resident intern midwifery assistant at St. Bartholomew's Hospital, and then, having proceeded M.D. in 1924, he became house-physician at the London Chest Hospital.

In 1926 Jeaffreson went to the Jessop Hospital for Women, Sheffield, where he worked for two years under Professor Miles Phillips and where he began in earnest his career in obstetrics and gynaecology. In 1928, while working in Birmingham as assistant to the late Sir Beckwith Whitehouse, he obtained the F.R.C.S., and in 1930 he went to Leeds as tutor in obstetrics and gynaecology, later becoming senior clinical lecturer in gynaecology in the university. He told, always with amusement, how a lay member of one of the committees which appointed him at Leeds gave voice to her thought that his travels had made him a rolling stone and that soon he would be moving on again. But he settled down to a brilliant career in Leeds, being appointed honorary assistant surgeon to the Hospital for Women in 1930 and becoming honorary surgeon to the Maternity Hospital in 1934. Jeaffreson was admitted a Member of the Royal College of Obstetricians and Gynaecologists in 1936, becoming a Fellow in 1950, and he served on the council of the College from 1942 to 1949. The work which interested him most was teaching, and indeed he was a great teacher. His lucid exposition and infinite patience endeared him to a large number of Leeds students. He himself had remarkable diagnostic powers, and he insisted on the painstaking elicitation of physical signs by his juniors. But his modesty in that, as in other respects, made the lesson on each occasion the more telling. If he will be honoured as a teacher, he will be remembered, particularly by his junior colleagues, as a kindly chief and an approachable friend.

He was a good organizer, and the success which attended the thirteenth British Congress of Obstetrics and Gynaecology, held at Leeds last year, was in no small measure due to his efforts as senior secretary. Many were looking forward to his term of office this year as president of the North of England Obstetrical and Gynaecological Society. He leaves a widow, and a son and a daughter.—A. V. G. B.

Sir T. DRUMMOND SHIELS, *M.C.*, M.B., Ch.B.

A. B. W. writes: "T. D.," as he was known to many of us who graduated with him at Edinburgh, had something about him which drew us to him. Perhaps it was his seniority in years and his wider background of experience, but in those early days we recognized those sterling qualities of heart and mind—his humanism, his kindly sympathy and understanding, his quiet courage and patience, his intellectual endowments, and his dry humour—which he put to such good use later in the service of his profession, his country, and the Commonwealth. His concern was never for himself but for others, especially those struggling with ill-health or adversity. He was a fearless espouser of lost causes, like that of Oscar Slater, if he felt that a wrong had been committed. A devoted husband, a loving father, staunch and true to his many friends, "T. D." was indeed one of Nature's "veray parfit" gentlemen. He passes to his rest leaving the world better and nobler by his efforts.

Dr. E. G. L. GOFFE, who practised for many years in Kingston-upon-Thames, died at Ferring, in Sussex, where he had lived in retirement for only a few months, on November 28, 1952, at the age of 85. Ernest George Leopold Goffe was born in Jamaica on September 12, 1867, the son of Mr. J. B. Goffe, J.P., and received his early education at York Castle High School, Jamaica. He then came to London and entered University College as a medical student, distinguishing himself as an athlete and as a rugby footballer. He graduated M.B. in 1897, and proceeded M.D. two years later. After holding a number of house appointments at University College Hospital he became assistant medical officer and later assistant medical superintendent at Lewisham Infirmary, subsequently holding posts at other hospitals in the London area. He then settled in practice at Kingston-upon-Thames and continued his hospital association by joining the staff of the Kingston Victoria Hospital, where his charm of manner and vast store of knowledge and experience endeared him to all his colleagues. The closure of the hospital to general practitioners in 1951 greatly saddened him. Dr. Goffe gave up general practice in June last year to enjoy a well-earned retirement, a retirement which proved to be tragically short. A member of the British Medical Association for 56 years, Dr. Goffe was chairman of the Kingston-upon-Thames Division in 1924–5, and he represented his constituency at the Annual Representative Meeting on six occasions. He married Edna Mary, daughter of the Reverend E. Pierce Powell, and she survives him, together with three sons. Mrs. Goffe is herself a member of the medical profession, and one of the sons is Dr. Alan Powell Goffe, also a medical practitioner.—T. W. M.

We are greatly indebted to Dr. DAVID NABARRO for the following appreciation: I first met Leopold Goffe more than 60 years ago, when I entered University College as a medical student in October, 1890. He had a fine physique which made him very noticeable in any assembly. A friend once remarked of him that he resembled a Greek god. His infectious laugh and his good humour made him a valuable acquisition to any company. In his student days he was a great athlete, and in 1892–3 he won the Quain challenge cup for athletic sports. He also played rugby football for University College Hospital from 1892 to 1894. Goffe was a great altruist. As an undergraduate he was very interested in the University College Boys' Club Society and attended the club every week to give the boys instruction in athletic sports. In the summer he helped to take them on their annual trip on the Norfolk Broads. He was also the honorary treasurer of the society. Further examples of his altruism in setting up and managing trusts for the sons of deceased colleagues will be well remembered by some of his friends. Goffe took the London M.D. in 1899, and at the presentation for degrees in May, 1900, at which the Prince of Wales—afterwards King Edward VII—distributed the prizes, I well remember the applause which greeted Goffe when he ascended the platform, a striking figure in scarlet and purple gown, to receive his degree from His Royal Highness. He was a most lovable man, and his patients must be considered fortunate to have had so good a doctor and so sympathetic a friend as their medical adviser. It was remarkable how he retained his interest in medicine to the end. Each year he attended the course for old students at University College Hospital, and 1952 was no exception. For several years we sat beside one another at the annual dinner, and it was only a few weeks ago that we sat alongside for the last time. And now this great man has gone to his rest, but his personality will endure. Our sympathy is extended to his widow and three sons in their bereavement, but theirs is the satisfaction of knowing that Leopold Goffe's name will live for many years in the affection of his multitude of patients and friends.

Dr. HILARY LEDGERWOOD, who died in London on December 6, was born on December 7, 1890, and was educated at Queen's University, Belfast, where she graduated M.B., B.Ch. in 1921. After holding a house appoint-

ment at Stanley Hospital, Liverpool, she settled in general practice in London. She became physician in charge of a maternity clinic in North Marylebone, and was for a time honorary assistant anaesthetist to the Metropolitan Ear, Nose, and Throat Hospital. Later she was appointed clinical assistant to the gynaecological department of the South London Hospital for Women and medical officer to a baby clinic in Kensington. Dr. Ledgerwood was the widow of the late Dr. Andrew Harman Pearce, who died in 1937. They were married in 1924.

A correspondent writes: Like society in general, the medical profession has grown poorer in characters in the Irish sense of this word. With the death of Dr. Hilary Ledgerwood it grows poorer still. Those who knew her in her college days when, after taking her degree in modern literature, she turned to medicine have always been aware of the literary quality that clung to her sayings and doings. It was a custom with convivial medical examiners to quote passages from Miss Ledgerwood's answers to questions; some of her papers were said to have been preserved. The casual might sometimes mistake her stylized wit for mere affectation, but her friends knew that her outward ways were the reflection of a real personality in which courage was always at war with almost painful sensitivity. Hilary Ledgerwood was beloved by many needy patients and by the friends who knew that, of all her impulses, generosity was the strongest. She will always be remembered by her own generation, but had she lived in an age more prolific of Boswells she would have been made immortal in medical legend.

Dr. GERTRUDE H. G. HICKLING died at her home at Newcastle-upon-Tyne on December 24, 1952, after a long illness, at the age of 69. Born at Blackpool on June 5, 1883, the daughter of the late Mr. H. Geiler, Gertrude Hermine Geiler was educated at the University of Manchester, where she graduated B.Sc. in 1906. Four years later she obtained the degrees of M.B., Ch.B., proceeding M.D. in 1912 and taking the D.P.H. in the same year. In 1910 she married Dr. H. G. A. Hickling, now emeritus professor of geology in the University of Durham. Dr. Gertrude Hickling lived most of her life in and around Manchester before moving to Newcastle-upon-Tyne in 1924. Her original aim had been medical missionary work, but that was rendered impossible of fulfilment because of severe rheumatic fever from which she suffered during her university career. After graduation her many interests were with children, and she was closely associated from 1910 to 1924 with the late Dr. Catherine Chisholm in child-welfare work, especially at Pendlebury Hospital and in helping to found the Manchester Babies' Hospital. In 1924 Dr. Hickling went to Newcastle-upon-Tyne with her husband, who had been a lecturer in the University of Manchester, and their young family, and from 1925 to 1929 she conducted a small Parents' National Educational Association school in her own home. Her association with the Newcastle-upon-Tyne maternity and child-welfare department began in 1930, when she joined the staff of part-time child-welfare medical officers, work which she continued to do until 1950, when she was forced to give up owing to ill-health. Besides her work for the local authority she did a great deal of voluntary work throughout her medical career. She was a founder member, and chairman for many years, of the Tyneside branch of the Nursery School Association of Great Britain, which, with the help of the British Federation of University Women, set up its first nursery school in Newcastle in 1929. The school provided work after her own heart, and she was honorary medical officer to several of the nurseries run by voluntary bodies both in Newcastle and in Gateshead. During the last war, besides taking on extra child-welfare duties under the local authority, she undertook some anaesthetic work at one of the local hospitals. It was probably due to those years of overwork and strain that her health broke down shortly after the war. Her friends always felt that her will to do was much stronger than her physical capacity would allow. Although a small, frail figure in later years, she remained a strong personality, young in mind and spirit. Her selfless work, her kindness, and her thought for others endeared her to many more than she ever realized, particularly among the poorer people on Tyneside when unemployment was rife during the years of depression. Our sympathy goes out to her husband, Professor Hickling, and to their son and two daughters.—S. M. L.

Dr. DONALD CAMPBELL BUCHANAN, who died at Glasgow on December 24, 1952, at the age of 62, was born at Taynuilt, Argyllshire, on June 4, 1890, and was educated at the University of Glasgow, where he was a very popular student. After a distinguished career he graduated M.A. in 1912 and proceeded to medicine, but his studies were interrupted by the outbreak of war in 1914, when, as a member of the Special Reserve, he was commissioned to the Seaforth Highlanders and went to France with his regiment. He was subsequently sent back to Glasgow to finish his medical course, and, after obtaining the degrees of M.B., Ch.B. in 1917, he served as a captain in the R.A.M.C. in East Africa, where he was surgeon at the K.A.R. Military Hospital at Nairobi, until the end of hostilities, being twice wounded. When Dr. Buchanan returned to civilian life he settled at Rutherglen, where he built up an extensive practice. He had obtained a commission as flight-lieutenant in the Auxiliary Air Force in May, 1939, and when war came again in the following September he was called up for full-time service. He was promoted squadron-leader in 1940. After a period in this country he saw service in East Africa and in the Middle East, but his several applications to serve with the Desert Forces in Egypt were rejected on account of his age, rejections which disappointed him sorely. In all he served four years overseas. After the war Dr. Buchanan returned to his practice at Rutherglen with his health somewhat impaired. He did not complain, but he was no longer a man of great physical strength, and he lacked the robust vigour which his friends had always associated with him. He could be described as a restless idealist with but one aim in life, to help his fellows. Of great intellectual capacity, he had accumulated a fund of masterly knowledge and experience in medicine, and he was an ardent Celtic scholar with a great love of the Gaelic language and literature. His loss will be mourned and his memory honoured by many colleagues and friends. He leaves a widow, to whom we offer our sincere condolence and deepest sympathy.—D. F.

By the death of Dr. LLOYD W. HUGHES on December 26, 1952, at the age of 63, South Caernarvonshire has lost a kindly and a conscientious practitioner. Lloyd William Hughes was born at Blaenau Festiniog on July 19, 1889. He completed his medical education in Scotland, and after qualifying in 1917 he served as a captain in the R.A.M.C. in the last two years of the war of 1914–18. In 1921 he settled in practice at Bottwnog, in succession to the late Dr. Edward Thomas. The extensive rural area in which he worked included the island of Bardsey, and from time to time he had to cross Bardsey Sound to attend to some of his patients. He had been in indifferent health for the last few years, a fact which obliged him to decline the presidency of the North Wales Branch of the British Medical Association some years ago. For many years he was medical officer to the old Board of Guardians of Pwllheli, and he was a former governor of Bottwnog Grammar School and a county councillor. It is possible that the rigours of country practice and the conscientiousness with which he carried out his work were contributory factors to his comparatively early death. His patients mourn a friendly and beloved physician, and his colleagues a practitioner who maintained the highest standard of medical ethics. Our sympathy goes out to his widow and to his two daughters and three sons, the eldest of whom was in partnership with his father, and who carries on his fine tradition.—H. H. J.

The sudden death on December 27, 1952, of Mr. CHARLES HAROLD MEDLOCK, or "Pop" as he was affectionately called by nurses and house officers, at the age of 64, has removed a familiar and popular figure from the North-east Metropolitan Region and especially from the Hertford County Hospital, which was his second home for the last 28 years. Born in London on September 12, 1888, the son of Mr. William Medlock, he was educated at University College School and at Guy's Hospital. In his youth he excelled in many branches of sport and represented his hospital at rugby football, cricket, and athletics. He also played cricket for the Public Schools against the M.C.C. at Lord's and had been captain of the Guy's Hospital and the Middlesex county rugby football teams. In the National Territorial Sports he distinguished himself by winning the long-jump championship three years running, from 1912 to 1914. Before qualifying M.R.C.S., L.R.C.P. in 1915 he served in the war of 1914–18 as a dispatch rider but was granted "leave on duty" to complete his medical studies at Guy's. He later entered the R.A.M.C., attaining the rank of captain, and served in France from 1917 to 1919 as medical officer attached to the 4th battalion of the Tank Corps. He was mentioned in dispatches in 1919. From 1919 to 1924 he held various appointments at Guy's Hospital, and while there he obtained the F.R.C.S. in 1924, in which year he joined the late Dr. Ernest Ravensworth Hart in general practice at Hertford. He became assistant surgeon to the Hertford County Hospital, and from 1929 to 1948 he was its senior surgeon. He was also consulting surgeon to Ware Park Sanatorium, the East Herts Infectious Diseases Hospital, and the Brocket Hall and Pear Tree maternity hospitals. In 1935 he gave up general practice for consultant work, and in 1948 he relinquished all general surgical work in order to concentrate on his appointment of consultant in obstetrics and gynaecology in the Hertford group of hospitals. Keenly interested in medico-political and committee work, he was chairman of the East Herts Division of the British Medical Association in 1934–5. He was also chairman of the medical advisory committee of the group and was a regular attender at the house-committee meetings. His colleagues always chose him as their representative because of his absolute integrity and for the happy way in which he could explain matters not readily understood by lay members of the board. The nursing staff will remember him for his kindness and courtesy and for the excellence of his surgical lectures, and there are many grateful patients who will hear of his passing with regret. If he had one fault it was over-conservatism; but some of his more enterprising colleagues have had to admit that the results he obtained were often as good as, if not better than, those achieved by more drastic measures.—W. D. B.

Dr. A. M. WARE, who died at the age of 78 at his home at Guildford on January 5, came of a family of medical men, of whom the most notable was James Ware, F.R.S., a distinguished eye surgeon and one of the foundation members of the Medical Society of London. Arthur Maitland Ware was born in 1874, the younger son of Mr. Martin Ware, a barrister, and was educated at Haileybury and Pembroke College, Cambridge, where he obtained a half blue for hockey and graduated B.A. in 1895. His medical education was at St. Bartholomew's Hospital. He qualified in 1899 with the Conjoint diploma, and in the same year took the degrees of M.B., Ch.B., proceeding M.D. in 1903 with a thesis on malignant endocarditis. After holding resident appointments at Bart's and the Birmingham General Hospital, Dr. Ware went into general practice in Kensington. Here he was to remain, an active and well-loved figure, for over thirty years, with only one short interruption when in 1914 he was with the B.E.F. in France. Later, at the end of the war, he was medical officer to the British delegation to the Versailles Peace Conference. During a busy professional life he found time for much voluntary work, both with the Order of St. John, of which in 1934 he was made a Knight of Justice, and in other directions. He was for many years a member of the governing body of the Shaftesbury Homes, and a vice-president of the Society for the Relief of Widows and Orphans of Medical Men. A professional appointment he particularly enjoyed was that of honorary physician to the Royal College of Music. After his retirement he went to live near Guildford, but even then he did not give up medical work entirely. During the war and until quite recently he was sitting on medical boards. In 1909 he married Edith Frances Maude. It was a happy marriage, and death came to him within a month of that of his wife. He is survived by two daughters.

C. V. N. writes: After leaving Bart's Arthur Ware started in practice in South Kensington, where he continued until 1935, when he retired and went to live on the hills outside Guildford. He was very popular with his patients, and, perhaps because of his attractive personality, the majority of them were likeable and interesting people. He was a perfect gentleman and the best type of family doctor and friend. You could be quite certain he would not let anything happen to you that medical skill could prevent. If he could not give some specialized service himself he would do the very best for you. He was very loyal to his professional brethren, and one never heard an adverse criticism from them. A Knight of Justice of the Order of St. John of Jerusalem, and for many years a member of Chapter General, he was keenly interested in all the beneficial activities of that ancient institution.

Mr. ARTHUR TWELFTREE, formerly chief clerk in the secretarial department of the Association, died in hospital at Worthing on January 15, at the age of 59. After military service in the first world war, Mr. Twelftree joined the staff as a committee clerk in 1919. He succeeded the late Mr. Coulson as chief clerk in 1937. In 1941 he was awarded the M.B.E. for his services to the Central Medical War Committee. He became seriously ill in the summer of 1950 and was unable to resume work until March, 1951. A recurrence of his illness in December of the same year led to his resignation, on medical advice, at the end of May, 1952. His death after a further short illness has come as a sad shock to his many friends in the Association who had hoped that, released from his arduous duties at B.M.A. House, he might enjoy many happy years in the new Sussex home to which he had moved.

The SECRETARY of the Association writes: Twelftree, throughout his many years of service, identified himself completely with the interests of the Association. He lived for the B.M.A. He had a complete mastery of the Association's constitution and procedure which made him a tower of strength to the members of the Secretariat, who were often assisted by his mature experience and shrewd judgment. Himself efficient, he expected efficiency in others, but it was a benevolent rule that he exercised as captain of a large clerical team, and in his dealings with subordinates he was always actuated by a sincere desire for their welfare and happiness. Their feeling towards him is shown by a remark of one of them: "I feel that I have lost not only an old colleague but also a true friend." Perhaps he was seen at his best in the turmoil of the Annual Meeting. Here his calm control did much to promote the smoothness of the "back-room" arrangements which drew so many congratulations from Representatives and overseas observers. There are many, not only on the staff, but also among present and former members of the central committees, the Council, and the Representative Body, who mourn his untimely death and extend their warm sympathy to his widow and son. To those who were intimately associated with him in the work of the Headquarters office he has left a happy memory of a most genial and kindly personality and an inspiring example of single-minded devotion to duty. The Association never had a more good and faithful servant than "A. T."

Universities and Colleges

UNIVERSITY OF LONDON

The following candidates have been approved at the examinations indicated:

M.D.—*Branch I (Medicine):* P. J. Banks, A. F. Barnett, H. Barrie, B. Bass, Mary Bateman, S. I. Cohen, Phyllis M. E. Cook, Betty B. Dyer, F. R. Ellis, D. G. Evans, D. M. D. Evans, D. D. Felix Davies, I. T. Gabe, P. J. D. Heaf, Cherry D. Heath, B. W. Jaslowitz, R. P. V. Jayewardene, A. M. Johnson, J. C. Leonard, W. E. Medd, L. P. A. Newborne, C. P. Newcombe, B. E. C. Nordin, M. A. Pears, Betty E. Powe, S. J. G. Semple, R. G. Shorter, K. A. Sowden, C. J. Stevenson, F. Taylor, W. B. Thomson, Brenda D. Van Leuven, B. W. Webb. *Branch II (Pathology):* A. Bernstein, J. L. Brennan, Patricia C. Brown, L. H. Collier, H. R. Colquitt, J. C. Crook, Phyllis Dagnall, D. Marrack, D. J. O'Brien, F. R. Philps, K. A. Porter, J. I. Pugh, M. V. Salmon, W. J. L. Sladen, C. S. Treip, S. P. B. Way, W. J. Williams, A. L. Woolf, E. A. Wright. *Branch III (Psychological Medicine):* A. A. Cashmore, J. Denham, A. Folkson, W. P. Gurassa, J. Merry, D. J. Parr (Mark of Distinction, University Medal), H. P. Tarnesby, D. L. C. Thomas, G. C. Turle. *Branch IV (Midwifery and Diseases of Women):* J. C. Brace, S. Burke, F. Denny, J. Elstub, G. W. Garland, D. W. S. Gordon, J. M. Holmes, R. Moolan-Feroze, Elsie M. Sibthorpe, N. G. G. Talbot. *Branch V (Hygiene):* J. D. B. Andrews, J. R. Mayers, Anita J. Thomas. *Branch VI (Tropical Medicine):* J. C. L. Adams, P. B. Adamson, A. C. S. Hobson.

The following candidates at the London School of Hygiene and Tropical Medicine have been approved at the examination indicated:

ACADEMIC POSTGRADUATE CERTIFICATE IN PUBLIC HEALTH.—I. Ash, Dorothy J. Ball, S. Bano, Mary M. M. Boyd, D. E. Boye-Johnson, R. Bradley, J. H. Brodie, P. P. M. Browne, Gwen S. Clark, J. Clearkin, C. Eid, A. J. Essex-Cater, R. S. Gibson, L. P. Harington, I. K. Hay, G. B. Hopkins, I. A. Hussein, Dorothy D. Jones, F. R. S. Kellett, A. J. I. Kelynack, S. Khuri-Otaqui, J. H. Lewis, K. H. Lim, B. Mahadevan, Mavis H. Mortimer, H. Mowschenson, A. Natarajan, F. G. Neild, B. Nicholson, W. L. Palmer, G. A. Real Jimenez, E. P. Rigby, W. F. Ross, M. C. Sanyal, J. H. Taylor, M. Tha Tun, D. E. Thompson, A. M. Thomson, D. R. Thomson, G. F. Willson, A. B. Wittek, C. H. Wood, A. Zahra, A. A. Zaki.

Dr. Mary F. Lockett has been recognized as a teacher of physiology and pharmacology in the University at the Chelsea Polytechnic. (*Corrected announcement.*)

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on January 8, with Sir Cecil Wakeley, President, in the chair, the Cecil Joll Prize for 1953 was awarded to Mr. Geoffrey Keynes. A Laming Evans Research Fellowship was awarded to Dr. Angus McPherson for his research into the blood-flow changes in the limbs in poliomyelitis. A Hunterian Professorship was awarded to Professor H. R. Dew for a lecture to be delivered during his visit as Sir Arthur Sims Commonwealth Travelling Professor in 1953. Erasmus Wilson Demonstratorships were awarded to Mr. V. E. Negus, Sir Frank Colyer, and Dr. B. E. Heard, and an Arnott Demonstratorship to Mr. L. E. C. Norbury.

The following were elected to the Fellowship of the Faculty of Anaesthetists: Dr. J. G. Bourne (Salisbury), Dr. H. G. Epstein (Oxford), Professor Fernando Hudon (Quebec), Dr. J. V. Mitchell (Oxford), Dr. G. Jackson-Rees (Liverpool), Dr. Arnold Robertson (Brisbane), Dr. A. Slater (New Zealand), Dr. B. N. Sircar (Bombay).

Diplomas of Membership were granted to A. G. N. Calder (Middlesex), K. G. Lupprian (St. Thomas's), and N. E. Pitts (Sheffield).

Diplomas were awarded, jointly with the Royal College of Physicians of London, as follows:

DIPLOMA IN ANAESTHETICS.—D. E. Argent, A. Banerjee, D. W. Barron, M. McC. Burrows, K. B. Chambers, C. C. D. Chandler, H. S. Cohen, E. A. Cooper, J. S. Crawford, D. W. J. Cullingford, L. D. Davidson, B. H. Egerton, S. Galloon, Rosalinde J. Harrison, Pamela M. Hellings, Frances S. Huxley, E. G. A. Jackson, J. W. Latham, R. A. L. Leatherdale, S. McKechnie, A. V. McVey, A. H. B. Masson, R. A. Millar, A. C. Milne, P. R. H. Molesworth, Ruth Molphy, E. J. O'Mullane, Doreen B. Pallot, J. Parkhouse, C. Pearce, D. J. Pearce, S. Ponnambalam, L. T. Rees, P. W. H. Robinson, F. M. Sandford, P. H. Simmons, W. D. Turner, D. C. White.

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—T. L. Bradbeer, D. C. J. Carter, G. O. Clark, D. A. Clements, J. B. David, J. W. T. Dixon, A. K. Ghosh, H. V. Jones, K. V. Krishnamurthy, J. Lapper, J. Littlejohn, A. Majali, J. S. Martin, H. W. H. Shepherd, D. W. Stuart, J. K. Suryodayam.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—R. H. Boardman, K. N. Kothaneth, T. R. Malloy, T. L. Pilkington, J. W. Warboys.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—H. Barakat, M. S. Boparai, T. Mirza.

DIPLOMA IN PATHOLOGY.—J. N. Dearnaley, J. S. Elwood, M. M. Friedman, E. M. Stirk, Jean E. D. Taylor.

DIPLOMA IN CHILD HEALTH.—A. Banerjee.

Hospitals were recognized under paragraph 23 of the F.R.C.S. regulations as follows: Royal Hospital, Wolverhampton, *Paragraph 23c*, senior registrar (senior house officer); house officer. Doncaster Royal Infirmary, *Paragraph 23c*, ear, nose, and throat house-surgeon (senior house officer). Barnet General Hospital, two house-surgeons (general surgery); house-surgeon (orthopaedics), all for six months. Haymeads Hospital, Bishop's Stortford, senior house officer (surgical) for six months. Royal Surrey County Hospital, Guildford, *Paragraph 23b*, ophthalmological and neurological senior house officer. Harrogate and District General Hospital, *decennial revision*, registrar, general surgery; registrar, orthopaedics; two house-surgeons, all for six months. Croydon General Hospital, principal surgical officer (or senior surgical registrar); surgical registrar, both for one year. St. Bartholomew's Hospital, Rochester, casualty house-surgeon (January 1, 1954). Gravesend and North Kent Hospital, casualty officer (January 1, 1954). St. Mary's Hospital, Portsmouth, *extension of temporary recognition until January 1, 1954*, senior surgical registrar; surgical registrar, each for 12 months; house-surgeon (general surgery and orthopaedics); house-surgeon (general surgery), each for six months. Clare Hall Hospital, Barnet, registrar (surgical); senior house officer (surgical), each for six months. Southport General Infirmary, *revision*, registrar (in place of senior registrar); two house-surgeons for six months (until January 1, 1954). Queen Elizabeth Hospital, Gateshead, house officer; surgical registrar, both for six months. Sunderland General Hospital, *additional recognition*, first house-surgeon for six months. Ryhope General Hospital, Sunderland, first house-surgeon; senior house-surgeon, both for six months. Mayo Hospital, Lahore, three registrars and six house-surgeons for six months (for one year). Central Middlesex Hospital, *decennial revision*, two registrars (general and neurology); one registrar (general and urology); one registrar (general and orthopaedics), all for one year; three house-surgeons (general and neurology); two house-surgeons (general and urology); one house-surgeon (orthopaedics), all for six months. *Casualty posts*, two senior house-surgeons, casualty, from January 1, 1954. Doncaster Royal Infirmary, *Paragraph 23b*, ophthalmic house-surgeon. Royal Homoeopathic Hospital, London, *decennial revision*, house-surgeon (general) for six months. St. Martin's Hospital, Bath, *additional recognition*, orthopaedic house-surgeon for six months. Cheltenham General Hospital, *decennial revision*, resident surgical officer, two house-surgeons, all for six months. King Edward VII Hospital, Windsor, *decennial revision*, surgical registrar for one year; first, second, and third house-surgeons for six months. *Casualty posts*, casualty officer (senior house officer), from January 1, 1954.

Vital Statistics

Infectious Diseases

A large rise occurred in the incidence of infectious diseases in England and Wales during the week ending January 3. The numbers of notifications always rise in the week after Christmas, compensating for the fall recorded in the preceding week, but the rise recorded this year is larger than usual. The increase included 16,308 for measles, from 14,189 to 30,497, 1,048 for whooping-cough, from 1,117 to 2,165, 597 for acute pneumonia, from 826 to 1,423, 358 for scarlet fever, from 1,358 to 1,716, and 78 for dysentery, from 184 to 262.

The rise in the incidence of measles was mainly concentrated in and around London. The largest increases were

London 1,709, from 996 to 2,705, Middlesex 1,723, from 784 to 2,507, Essex 1,347, from 1,415 to 2,762, and Kent 1,282, from 771 to 2,053. The largest rises in the number of notifications of whooping-cough were 137 in Essex, from 41 to 178, and 106 in Middlesex, from 31 to 137. The only large rises in the incidence of scarlet fever were Lancashire 60, from 170 to 230, and Essex 41, from 85 to 126. 25 cases of diphtheria were notified, one fewer than in the preceding week.

No case of paratyphoid fever and only 1 case of typhoid fever were notified during the week. This is the lowest level of the enteric fevers for almost three years.

During the week 37 cases of acute poliomyelitis were notified. These were 3 fewer for paralytic and 7 more for non-paralytic cases than in the preceding week. The largest returns were Sussex 5 (Chichester R.D. 3), Berkshire 3, Nottinghamshire 3, and Derbyshire 3.

The largest centres of infection for dysentery were Lincolnshire 53 (Grimsby C.B. 47), Lancashire 39 (Liverpool C.B. 19), Surrey 36 (Carshalton U.D. 32), London 26, and Warwickshire 14.

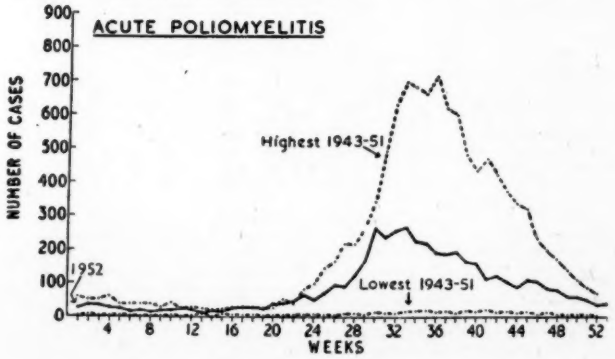
England and Wales in 1952

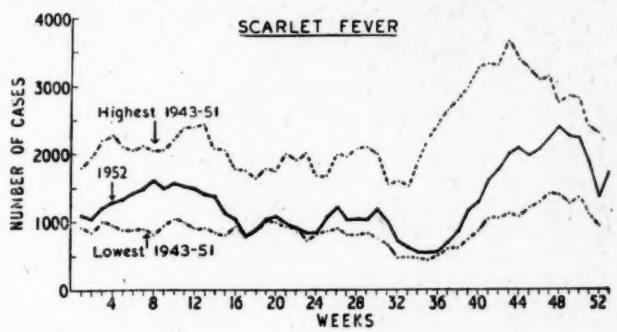
The chief feature of the returns of infectious diseases during 1952 was the absence of an outbreak of influenza in the spring. In the first 13 weeks only 485 deaths were recorded in the great towns from this disease, compared with 7,859 in the first quarter of 1951. The incidence of diphtheria continued to fall during 1952, but the rate of decline was slower. The notifications of diphtheria in 1952 were only 2.9% of the notifications in 1941. The total notifications of acute poliomyelitis were 46% above the total of 1951. The notifications of dysentery were about half the total of 1951, but the incidence remained high. The high level of the enteric fevers was mainly due to the persistent outbreak in South Wales during the third quarter. A comparison of the notifications with those of the four preceding years is given below :

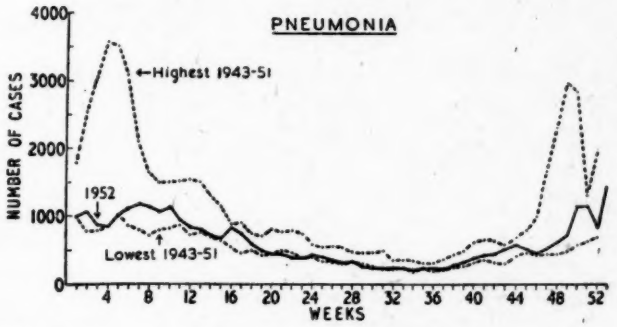
	1948	1949	1950	1951	1952
Scarlet fever	75,460	71,753	66,852	49,431	69,091
Whooping-cough	145,878	102,516	157,714	169,394	116,311
Diphtheria	7,903	4,929	2,858	1,969	1,473
Measles	396,841	384,361	366,116	615,332	400,838
Acute pneumonia	31,096	34,624	30,714	43,181	31,403
Meningococcal infections	1,971	1,586	1,745	1,956	1,687
Acute poliomyelitis	2,175	6,850	8,699	3,093	4,504
Dysentery	5,587	4,819	18,135	29,488	15,665
Typhoid and paratyphoid fevers	873	1,138	654	1,438	1,190
Deaths from influenza in the great towns	?	?	2,052	8,338	1,019

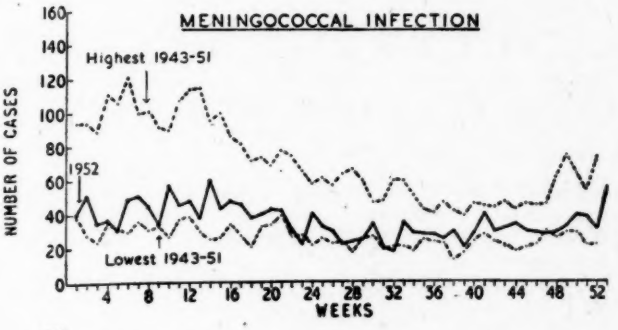
Graphs of Infectious Diseases

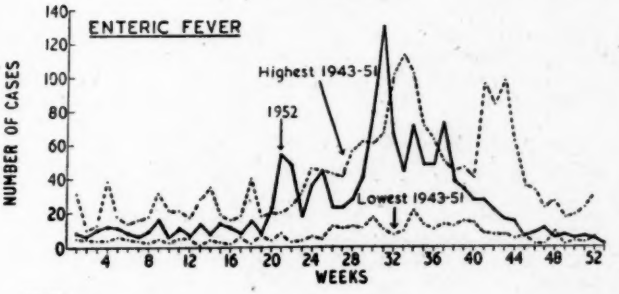
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1943–51 are shown thus - - - - - -, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

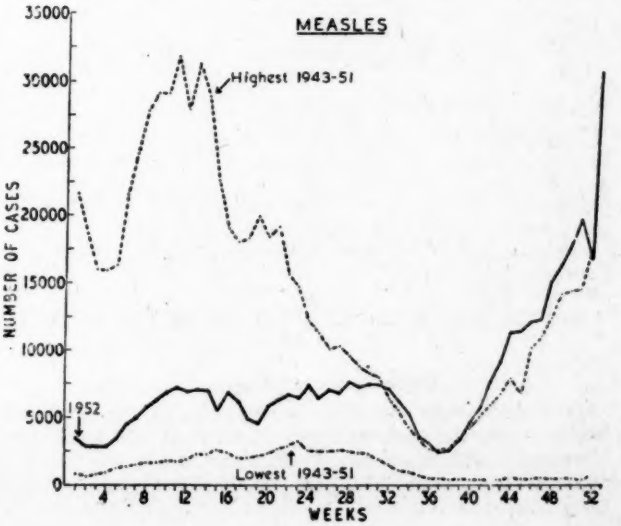


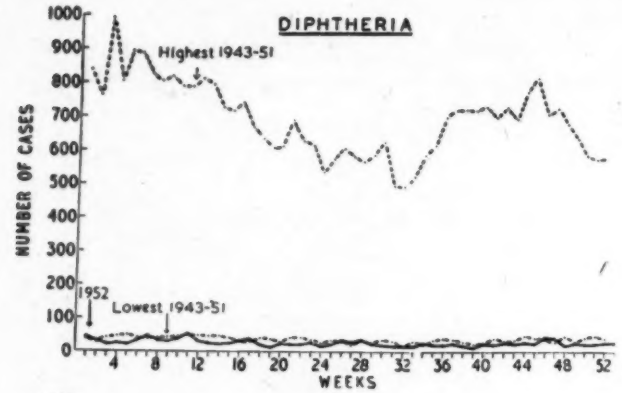


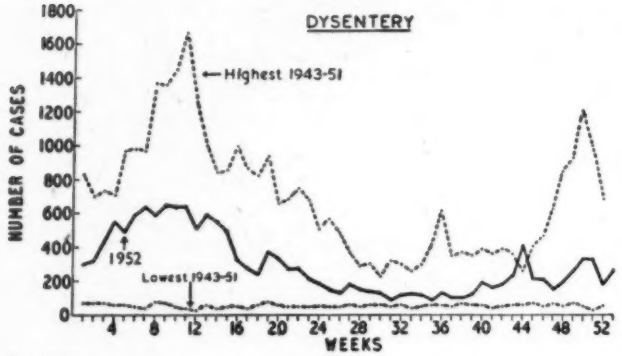


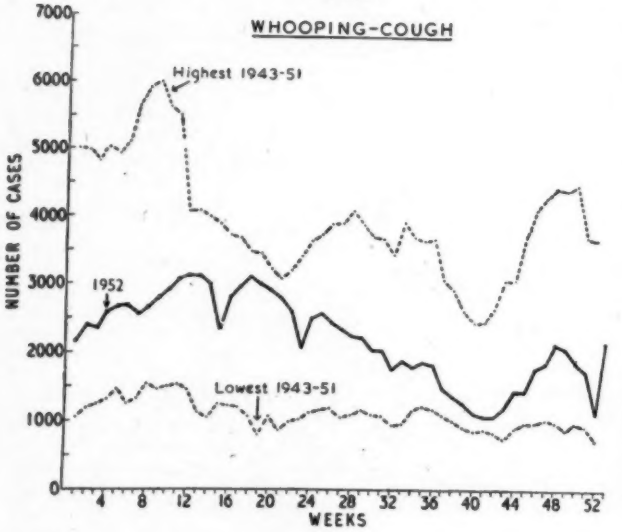


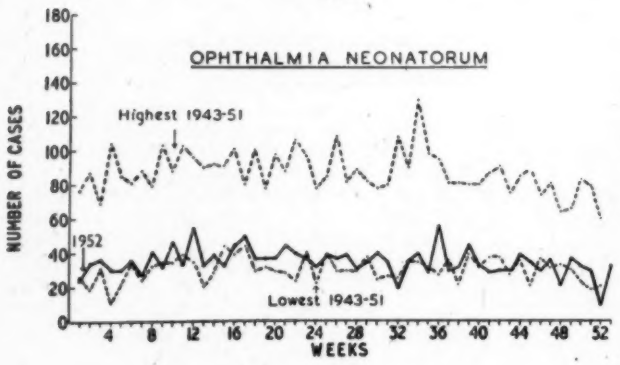












Week Ending January 10

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,238, whooping cough 2,060, diphtheria 22, measles 24,738, acute poliomyelitis 34, dysentery 214, paratyphoid fever 2, and typhoid fever 0.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending January 3 (No. 53) and week No. 52 of 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	25	3	4	1	0	43	3	13	0	2
Dysentery	262	26	63	2	7	293	17	84	0	
Encephalitis, acute	6	0	0	0	0	0	0	0	0	
Enteric fever:										
Typhoid	1	0	0	0		3	2	1	0	0
Paratyphoid	0	0	0	0		7	0	1 (B)	1	
Food-poisoning	47	15		0		449	7		0	
Infective enteritis or diarrhoea under 2 years				11	12				14	9
Measles*	30,497	2705	111	44	110	2,331	19	84	106	42
Meningococcal infection	55	7	16		2	26	4	15	1	1
Ophthalmia neonatorum	32	2	5	1		20	0	9	0	
Pneumonia†	1,423	131	243	9	2	678	30	245	4	
Poliomyelitis, acute:										
Paralytic	27	1	2	5	2	17	2	3	0	
Non-paralytic	10	0				3	0			
Puerperal fever§	220	29	6	4	0	131	21	13	1	
Scarlet fever	1,716	102	252	36	75	1,095	72	281	12	41
Tuberculosis:										
Respiratory			107	25				142	18	
Non-respiratory			16	4				29	8	
Whooping-cough	2,165	109	68	44	112	1,402	73	230	60	22

DEATHS in Great Towns	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	0	0	0	0	0	*1*	0	*1*	0	0
Dysentery	0	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	25	4	2	0	0	*12*		*3*	0	2
Influenza	29	4	2	0	3	*22*	5	*0*	0	0
Measles		1	0	0	0		0	*0*	0	0
Meningococcal infection		0	0				0	*1*		
Pneumonia	510	104		8	11	*250*	44		7	6
Poliomyelitis, acute	3	0			0	*0*	0			0
Scarlet fever		0	1	0	0		0	*0*	0	0
Tuberculosis:										
Respiratory	179	24	10	3	3	*131*	11	*28*	10	5
Non-respiratory		1	4	3	6		0	*2*	0	0
Whooping-cough	3	1	0	0	0	*0*	0	*2*	1	0
Deaths 0–1 year	342	47	33	14	17	*217*	30	*35*	4	9
Deaths (excluding stillbirths)	7,842	1372	709	157	253	*5,033*	816	*612*	115	104
LIVE BIRTHS	8,668	1235	708	240	468	*5,082*	707	*804*	138	91
STILLBIRTHS	202	20	20			*159*	25	*34*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Preparations for the Sixth World Health Assembly.—Under its chairman, Colonel M. Jafar, Director-General of Health, Pakistan, the Executive Board of the World Health Organization began on January 12 its preparatory meeting for the Sixth World Health Assembly. The Assembly is due to start on May 5 in Geneva. Two matters of special importance were raised in the chairman's opening speech. First, as one of the agencies of the United Nations Technical Assistance Programme, W.H.O. has been asked to cut down expenditure on its existing projects. Colonel Jafar outlined the consequences of this step to Governments already participating in specific health projects—"it would be an impossible situation to tell them now that W.H.O. cannot meet its commitments any more." Secondly, there was the question of nominating a successor to Dr. Brock Chisholm as Director-General of W.H.O. (see *British Medical Journal*, December 20, 1952, p. 1368). It was decided to hold a private meeting of the board for this purpose on January 26.

League of Hospital Friends.—Speaking at the annual meeting of the National League of Hospital Friends, which was held at St. Bartholomew's Hospital on January 14, the Minister of Health, Mr. Iain Macleod, said that, following the meeting a year ago which was addressed by his predecessor, Captain Crookshank, a personal link had now been established between the Ministry and the League, and he hoped the link would never be broken. He wanted to clarify the attitude of the Ministry to a problem that might in some localities be causing difficulties. He had been told that here and there it was thought undesirable for the chairman or members of a hospital management committee to take the initiative in forming a group of the League of Hospital Friends. He himself could not see that it was wrong in any way, and he liked to think that no chairman would regard his hospital or group of hospitals as complete until it had working within it such a loyal and efficient group. Mr. Macleod added that in future the National League would be one of the bodies to be consulted about appointments to regional hospital boards and boards of governors.

Home Care of Old People.—The Royal College of Nursing, the Queen's Institute of District Nursing, and the National Old People's Welfare Committee have united to produce a most valuable pamphlet of simple instructions for those, particularly relatives, who are responsible for the care of old people in the home. Written in a very direct and easy style, the pamphlet first describes the local services available for the help of old people, and then tells how to look after old people both when they are up and about and when they are confined to bed. There are separate sections dealing with incontinence and the prevention of accidents. In the words of the preface, the pamphlet contains "simple advice which, if acted upon, may make old people happier and more comfortable." Copies may be obtained, price 2d. each (plus postage), from the Royal College of Nursing, Henrietta Place, Cavendish Square, London, W.1.

Nuffield Lodge.—The removal of the headquarters of the Nuffield Foundation, the Nuffield Provincial Hospitals Trust, and the National Corporation for the Care of Old People to Grove House, Regent's Park, London, N.W.1, takes place on January 24 (see *British Medical Journal*, September 6, 1952, p. 571). Grove House, which is the large mansion opposite St. John's Wood Church, has been renamed Nuffield Lodge with the consent of the Commissioners of Crown Lands. The telephone number is Primrose 8871–5. The address of the Trust's Investigation into the Function and Design of Hospitals will be 33, Doughty Street, London, W.C.1 (Terminus 5288).

New Journal of Embryology.—The Company of Biologists Ltd., the non-profit-making agency founded many years ago at Cambridge to publish the *Journal of Experimental Biology*, is launching a new quarterly in the spring. The journal is the *Journal of Embryology and Experimental Morphology* (*J. Embryol. exp. Morph.*). It will be edited by Mr. M. Abercrombie, reader in embryology at University College, London, assisted by an editorial board of international composition. The journal will be in English (although some articles in French or German may be printed) and will include work on embryogenesis, growth and developmental processes in the older organism as well as studies on foetal–maternal relationships. The printers are the Clarendon Press. The promoters believe that the new journal will fill "one of the more striking gaps" in the list of scientific periodicals.

The "Medical World."—The *Medical World*, which until the end of 1952 was the weekly journal of the Medical Practitioners' Union, is now to appear monthly as a journal of general practice. Members of the M.P.U. will receive with their copy of the *Medical World* a medico-political supplement. The January issue of the new journal has now been published. Dr. Richard Scott is the author of the opening paper, which is a discussion of some factors affecting the quality of medical care, and the last of the signed contributions, beginning some 80 pages later, is a "Letter from France" by Dr. Gabriel Mouchot. A mixed bag of articles appears in the intervening pages, ranging from "Carcinogens in Alumina Reduction" by Dr. S. K. Livingston, who has investigated the occurrence of warts on the skin of certain factory workers, to "Medicine's Poor Relations," in which Mr. Kenneth Walker describes some examples of primitive medicine.

Research on Vitamins.—The National Vitamin Foundation Inc. announces new grants, valued at $61,500, to American university scientists working on vitamins. Most of the grants are to support studies on the B vitamins, particularly B_{12}. The National Vitamin Foundation, which in 1946 replaced the earlier Vitamin Research Institute, is an American agency financed by the vitamin industry for promoting research and correlating information on vitamins. Since its inception the Foundation has provided $635,180 for research. The grants are not limited to work done in the United States.

Francis J. Shepherd Memorial Lecture.—Sir Sydney Smith, Dean of the Faculty of Medicine at Edinburgh, will deliver the inaugural Francis J. Shepherd Memorial Lecture at McGill University, Canada, in the spring. This lecture, which is sponsored by the Montreal General Hospital, is to be an annual one, and will be delivered by eminent medical men from the United Kingdom. The Montreal General Hospital invited Sir Sydney Smith to be the first lecturer because the hospital was founded in 1821 by four Edinburgh graduates. The lecture will be on trends of medical education.

College of General Practitioners.—By January 15 more than 1,000 doctors had joined the newly formed College of General Practitioners.

The British Standards Institution is leaving its old home in Victoria Street, London, at the end of the summer and moving to more convenient accommodation in Mayfair. The new offices at 2, Park Street, to be known as "British Standards House," will allow greater centralization of staff as well as space for the 3,800 committee meetings convened by the Institute each year.

Sir Allen Daley, medical officer of health to the London County Council from 1939 to 1952, has gone to Australia for an eight-weeks tour of the State health services. The Nuffield Foundation is sponsoring the tour. Sir Allen will lecture to medical audiences and advise on public health problems. He is due to arrive at Melbourne on February 6.

Emergency Bed Service: Applications and Admissions.—During the seven days ending January 19 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,700, of whom 83.97% were admitted. A white warning, indicating that the percentage of admissions fell below 85, was issued on January 6.

COMING EVENTS

The British Council for Rehabilitation has arranged a one-day conference on "Speeding recovery through the closer co-operation of hospitals and industry," which will be held at the Royal College of Nursing, Henrietta Place, London, W.1, on February 4. The conference is intended for industrial medical officers and nurses. The fee is 15s., and bookings should be made in advance with the general secretary, British Council for Rehabilitation, Tavistock House (South), Tavistock Square, London, W.C.1.

Oxford Graduates Medical Club.—Sir Rudolph Peters, F.R.S., will take the chair at the winter dinner of the Oxford Graduates Medical Club at the Royal College of Surgeons on January 30 at 7 p.m. Tickets (price 30s.) may be obtained from Mr. Selwyn Taylor, 3, Roedean Crescent, Roehampton, S.W.15.

The Psychology of Eating.—The Scottish Group of the Nutrition Society will hold a conference on "The Psychology of Eating" in the Anatomy Lecture Theatre, Marischal College, Aberdeen, on January 31 at 1.20 p.m. Professor Rex Knight will be in the chair, and other speakers will include Professor W. M. Millar, Professor C. F. W. Illingworth, Dr. C. F. Rolland, Dr. J. M. Walker, and Dr. C. G. Kennedy.

SOCIETIES AND LECTURES

Details in this column are necessarily brief. Further information and tickets where required (marked ●) should be obtained from the institution concerned.

Monday, January 26

INSTITUTE OF PSYCHIATRY.—5.30 p.m., Dr. E. Stengel: Lecture-demonstration for postgraduates.

MEDICAL SOCIETY OF LONDON.—8.30 p.m., discussion to be introduced by Mr. W. J. Dempster, Mr. B. W. Rycroft, and Mr. A. L. Schofield: Present Status and Future Prospects of Homologous Tissue Transplantation.

Tuesday, January 27

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Sir Frederic Bartlett, F.R.S.: Nature and Place of Thinking in Medicine.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. Wade: Treatment of the Epithelioma.

LONDON UNIVERSITY.—At London Hospital Medical College, 5.30 p.m., Professor A. Claude (Brussels): Technical Aspects of Cell Research.

WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Nervous Disease: Part II.

Wednesday, January 28

CAMBRIDGE MEDICAL SOCIETY.—At Addenbrooke's Hospital, 8.15 p.m., A.G.M. Professor J. Dixon Boyd: "Pigment Cells" in Man.

EDINBURGH CLINICAL CLUB.—4 p.m., visit to Experimental Practice Dispensary, Richmond Street.

●ILLUMINATING ENGINEERING SOCIETY.—At Royal Institution, 6 p.m., Second Trotter-Paterson Memorial Lecture by Dr. E. D. Adrian, O.M., P.R.S.: Nervous Reactions of the Retina.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Precancerous Conditions of the Skin.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, W.C., 4.30 p.m., Dr. R. Thomson: Laboratory Aids to Diagnosis.

RENAL ASSOCIATION.—At 41, Portland Place, W., 4 for 4.30 p.m., Mr. A. W. Wilkinson: Biochemical Changes after Transplantation of the Ureters; Mr. D. Innes Williams: Long-term Results of Transplantation of the Ureters for Ectopia Vesicae.

ROYAL EYE HOSPITAL CLINICAL SOCIETY.—At Royal College of Surgeons of England, 8 p.m. demonstration of work of Ophthalmological Research Unit, Royal Eye Hospital, and Royal College of Surgeons of England.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Finlayson Memorial Lecture by Professor E. J. Wayne: The Heart in Endocrine Disease.

SOCIETY OF CHEMICAL INDUSTRY: FOOD GROUP—NUTRITION PANEL.—At Burlington House, W., 6.15 p.m., Dr. G. A. C. Herklots and Professor J. Yudkin: Food and the Future—Present Methods of Attack on the Problem.

Thursday, January 29

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Sir Alexander Fleming, F.R.S.: Recent Progress in Antibiotics.

EDINBURGH UNIVERSITY.—At University New Buildings, 5 p.m., Professor Jean Fiolle (Aix-Marseille): Diagnosis and Treatment of Embolisms of Arteries of the Limbs.

EPSOM AND SUTTON INTER-HOSPITAL PSYCHIATRIC ASSOCIATION.—At St. Ebbas's Hospital, 6 p.m., clinical meeting. Dr. H. H. Robinson: Combined Insulin Coma and E.C.T. Treatment; Dr. D. E. Sands: Some Observations on 200 Patients Treated by Leucotomy with the Use of Three Forms of Operation.

GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—At Glasgow University Union, 7.30 p.m., Mr. A. W. Kay: Ulcer Problem: The Quest for Achlorhydria.

●INSTITUTE OF CHILD HEALTH.—5 p.m., Mr. H. S. Sharp: Upper Respiratory Tract Disorders.

LONDON UNIVERSITY.—At London Hospital Medical College, 5.30 p.m., Professor A. Claude (Brussels): Morphological and Biochemical Aspects of Cell Structure and Function.

OXFORD UNIVERSITY.—5 p.m., Dr. G. W. Corner (Washington): Anatomical Illustration and the Fine Arts.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Sir Geoffrey S. Todd: Modern Methods in the Treatment of Pulmonary Tuberculosis.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Professor J. M. Mackintosh: Medical Care To-morrow.

Friday, January 30

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. G. B. Mitchell-Heggs: Acne Vulgaris, Acne Excoriée, and Dermatitis Artefacta.

ROYAL INSTITUTE OF PHILOSOPHY.—At University Hall, 14, Gordon Square, W.C., 5.15 p.m., Mr. D. A. Rees, M.A.: Greek Views of Nature and Mind.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Dr. K. W. Miller: Allergy.

UNIVERSITY COLLEGE.—At Physiology Theatre, 5.30 p.m., Professor F. Bergel: Some Chemical Aspects of Normal Growth.

APPOINTMENTS

EYTON-JONES, JACK, M.B., Ch.B., D.Obst.R.C.O.G., Obstetrical and Gynaecological Registrar, Scarsdale Hospital, Chesterfield, Derbyshire.

HAMMOND, GEOFFREY T., M.D., M.R.C.O.G., Consultant Obstetrician and Gynaecologist to Winchester Group of Hospitals.

NOTTINGHAM, CITY OF.—Elspeth M. Warwick, M.B., Ch.B., D.P.H., Deputy Medical Officer of Health; Patricia H. S. Shaw, M.D., D.P.H., Senior Medical Officer.

O'RIORDAN, J. P., M.B., B.Ch., D.P.H., D.C.H., Lieutenant-Colonel, I.M.S.(ret.), Port and Airport Medical Officer, Dublin.

RICE-OXLEY, J. M., D.M., M.R.C.P., Consultant Physician to the Chesterfield Royal Hospital and hospitals at Worksop and Retford.

ST. HILL, CHARLES A., M.B., Ch.B., Home Office Pathologist (Liverpool Region), attached to Forensic Science Department, Preston.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—A. E. Fyfe, M.B., B.S., Registrar in Obstetrics and Gynaecology, Southmead Hospital, Bristol; Z. L. Szur, M.B., B.Ch., D.M.R.D., D.M.R., Assistant Radiotherapist, Exeter Clinical Area; J. B. Gordon-Russell, M.B., Ch.B., M.R.C.P., D.P.M., Consultant Psychiatrist to South Somerset Clinical Area; R. J. Hart, M.B., B.S., Orthopaedic Registrar in North Gloucestershire Clinical Area.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Lewis.—On January 11, 1953, at The Maltins, Boars Hill, Oxford, to Dr. Evelyn, wife of Dr. Charles Lewis, a sister for Alexandra—Joanna Augusta.

DEATHS

Atkinson.—On January 14, 1953, Wilfred Percy Tindal Atkinson, M.R.C.S., L.R.C.P., of Old Manse, Fair Green, Sawbridgeworth, Herts, aged 68.

Browne.—On January 13, 1953, at the Bristol Royal Infirmary, Frederick William Browne, M.B., B.Ch., of Penhill, Shirehampton, Bristol.

Cooper.—On January 15, 1953, at Packhorse Cottage, Bessels Green, Sevenoaks, Kent, John Gerald Cooper, M.B., B.Ch., aged 78.

Cuthbert.—On January 17, 1953, at Dundee, James Arthur Cuthbert, M.B., Ch.B., D.P.H., of 247, Strathmartine Road, Dundee.

Elsner.—On January 12, 1953, at Desmesne House, Heighington, Darlington, Co. Durham, Otto William Alexander Elsner, C.B.E., D.S.O., L.R.C.P.&S.I. & L.M., D.P.H., Colonel, R.A.M.C., retired, aged 81.

Fowler.—On January 14, 1953, Henry Fowler, L.R.C.P.&S.Ed., L.R.F.P.S., of 160, Chislehurst Road, Orpington, Kent.

Grant.—On January 14, 1953, at his home, Hazel Coppice, West Mersea, Essex, Alexander Smeaton Grant, M.R.C.S., L.R.C.P., aged 83.

Hayman.—On January 9, 1953, at his home, Royden House, Sharnbrook, Beds, Frank Keith Hayman, M.B., F.R.C.S., formerly of Great Yarmouth, Norfolk, aged 59.

Lee.—On January 7, 1953, at his home, 7, Upper Maze Hill, St. Leonards-on-Sea, Sussex, James Carrel Lee, M.D., C.M., J.P.

McGregor.—On January 12, 1953, at the Princess Royal Hospital, Halifax, Yorks, Robert McGregor, L.R.C.P.&S.Ed., L.R.F.P.S., of Moor View, Walsden, Todmorden, Yorks.

March.—On January 14, 1953, Charles March, M.B., Ch.B., of The Little House, Gerrards Cross, Bucks, aged 40.

Martin.—On January 6, 1953, at Hampstead, London, N.W., Alfred John Martin, O.B.E., M.R.C.S., L.R.C.P., D.P.M., of Norgrove, The Bishops Avenue, London, N., aged 43.

Mosse.—On January 7, 1953, Cotton Grimley Tenison Mosse, M.R.C.S., L.R.C.P., of Southminster, Essex.

Robertson.—On January 6, 1953, at Banbury, Oxon, James Fenwick Robertson, M.R.C.S., L.R.C.P., aged 76.

Scott.—On December 8, 1952, at the National Hospital for Nervous Diseases, Queen Square, London, W.C., Philip Dennis Scott, M.B., B.S., of Clifton Hill, London, N.W., aged 61.

Wilson.—On January 14, 1953, at her home, Roseneath, Fairmount Road, Cheltenham, Glos, Sarah Wilson (formerly Kaye), M.B., aged 85.

Williamson.—On January 18, 1953, at 11, Chaffer's Mead, Ashtead, Surrey, John Rutter Williamson, M.D., aged 81.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Malaria Prophylaxis during Pregnancy

Q.—*What is the best malaria suppressive to use during pregnancy?*

A.—Chloroquine is probably the best suppressive for all forms of malaria during pregnancy. Proguanil and mepacrine are likely to be equally active against the parasites, but in the former case there is the possibility of having to deal with a proguanil-resistant strain of falciparum malaria, and in the latter the skin is stained yellow. If falciparum infection is suspected a full therapeutic course of chloroquine, mepacrine, or proguanil should be given before starting on the suppressive regime. None of these drugs is likely to affect the pregnancy. Quinine should be avoided because it is less efficient than the other drugs; in the dosage used for therapy or suppression it is not likely to affect the pregnancy.

Ellis Classification of Nephritis

Q.—*Is the Ellis classification of nephritis now universally accepted or is one still justified in using the old acute, subacute, chronic, etc.? Could you give me a résumé of the Ellis classification, including percentage of recovery or ultimate fate in each group? What is Ellis's view on "nephrosis," and is his view generally accepted?*

A.—The Ellis classification of nephritis has been widely accepted both in this country and abroad. It is more popular, on the whole, with clinicians than with pathologists. Reference to current textbooks shows that many pathologists still make use of the time-honoured terms: acute haemorrhagic glomerulo-nephritis, subacute and chronic nephritis, and so forth. This is due not to a reactionary bias on their part but to a certain scepticism arising from the frequent difficulty in reconciling the histological appearances with the clinical diagnosis of Ellis's Types I and II. In particular they observe, from time to time, that a nephritis may appear to start as Type I but proceed later to the clinical manifestations of Type II with retention of the glomerular features of Type I; there are many transition forms, histologically, between the two.

Ellis described his classification in his Croonian lectures on "The Natural History of Bright's Disease," which he gave in 1941. Type I nephritis mostly affects young subjects and corresponds to the "acute haemorrhagic nephritis" of older classifications. It is generally reckoned that from 80–85% recover completely; of the remainder a few die in the acute stage or the rapid progression of this to a "subacute stage." The remainder do not clear up completely but enter a latent stage, which may last for several decades, ending with contracted kidneys, secondary hypertension, and uraemia. Type II nephritis occurs over a wider age range, is of insidious onset, and characterized by the "nephrotic syndrome." The disease is steadily progressive, and recovery is rare. If death does not occur at an early stage from secondary infection the condition may progress, over months or years, to a stage of renal failure with secondary hypertension. If "nephrosis" is taken to signify the "lipoid nephrosis" of Munk, Volhard, and Fahr and others this would be included in Type II nephritis, but other forms of nephrosis such as the amyloid and mercurial forms are included in Ellis's "miscellaneous conditions." Apart from Type I and Type II nephritis Ellis also recognized a hypertensive group, in which "essential hypertension" is subdivided into "benign" and "malignant" groups. One does not speak of recovery in these, but the prognosis differs widely. In the malignant form the course is usually rapid, with death in less than two years; the benign is compatible with a normal life over many years, especially in women.

Slow Convalescence after Virus Infections

Q.—*To what is attributed the slow rate of recovery to full vigour from virus infections, such as pneumonia treated with chloramphenicol or similar antibiotics? What is the prognosis and treatment of protracted insomnia with which this prolonged convalescence is sometimes associated?*

A.—The rapid response of the toxaemia in virus infections of the lung following therapy with the new antibiotics makes it important to realize that return to normal vigour depends upon structural recovery of the affected part, a process which takes some weeks. The patient has had a severe illness, and convalescence should never be cut short however dramatic the initial response seems to be.

Protracted insomnia following these illnesses is part of a general state of depression, which is especially common after infection with the influenza virus. It is best treated by giving a mixture of amylobarbitone 1 gr. (65 mg.) and amphetamine sulphate 5 mg. in the morning and at midday, and an adequate dose of barbiturate at night. Quinalbarbitone 1½ gr. (0.1 g.) with amylobarbitone 3 gr. (0.2 g.) is generally suitable. The condition clears up as a rule within a few weeks.

Anaesthesia for Cataract Operations

Q.—*What is the best general anaesthetic for cataract operations?*

A.—It is difficult to lay down hard-and-fast rules about any anaesthetic—the choice depends so much on the patient, and the result on the skill of the anaesthetist. As postoperative vomiting, and straining and coughing, must be avoided the operation is usually performed under local analgesia; but general anaesthesia can be wholly satisfactory. For an "average" patient, 0.5 g. thiopentone and 40 mg. gallamine triethiodide can be given; the pharynx, epiglottis, and larynx are sprayed with 3 ml. of 4% cocaine by a Macintosh spray; a pharyngeal airway is inserted and nitrous-oxide–oxygen is given. The anaesthesia may be reinforced with a small quantity of trichlorethylene or intermittent doses of thiopentone, but if the customary local analgesic is given after the patient is asleep the depth of narcosis need not be deep.

Anosmia and Cacosmia

Q.—*What are the likely causes of loss of the sense of smell gradually following its perversion? This has occurred in an elderly man who has always been troubled with nasal catarrh. Now he cannot smell creosote or bonfires; formerly he thought he could smell fat frying and burning pastry when there was none. What investigations and treatment are advised?*

A.—Anosmia and cacosmia are usually the result of some local disturbance of the olfactory area of the nose itself. The commonest cause of anosmia is inability of the vapourized substances to reach the olfactory cells in the lining of the upper third of the mucous membrane lining the nasal cavity. It is usually a temporary accompaniment to the common cold and fortunately lasts only a few days. Sometimes it follows a very severe upper respiratory infection of the influenza type. Anosmia also occurs in cases where the nose is full of polypi. Some patients with allergic rhinitis, where there is much swelling of the mucosa, may also be unable to smell.

Cacosmia, or an abnormal olfactory sensation, is fortunately unusual. It may follow an upper respiratory infection or may appear for no reason at all. A few cases have been recorded in which it has followed the use of tyrothricin locally. An olfactory aura is not uncommon in epilepsy. Very occasionally tumours involving the olfactory tracts in the brain may give rise to abnormal olfaction or to loss of the sense of smell. In the case in question a full nasal and neurological examination is recommended. Apart from dealing with any disease in the nose no other form of local treatment is advised.

Risk of Transmitting Trichomonal Infections to Children

Q.—*A girl of 18, who is being treated for a Trichomonas vaginalis infection with a heavy purulent discharge, is in charge of a baby girl aged 1 year. Is the child likely to become similarly infected, and, if so, what precautions should be taken?*

A.—There is a good deal of evidence to show that trichomonal infection is transferred from one individual to another, but the exact mode of transfer is in most cases unknown. Newly born babies of infected mothers occasionally have *Trichomonas* in the vagina (R. E. Russell *et al., Amer. J. Obstet. Gynec.*, 1942, **44**, 292), and trichomonal vaginitis does occur in infancy and childhood. Nevertheless, considering how widespread is trichomonal vaginitis in adults, there are remarkably few cases of this infection in infancy. Even when groups of cases of vulvovaginitis in infancy are analysed, trichomonal vaginitis is a rare cause. Thus, although there is a risk of transfer of infection in a case such as the one described it must be extremely small.

As regards precautions, the first essential is to institute treatment for the nursemaid. The risk should also be explained to her, and she should be given strict instructions about always washing her hands thoroughly before handling the child, its clothing, and its napkins. The nurse's bedding, underclothes, and bath-towels should be kept separate, even during laundering, and she should not use the same bath as the baby—even though it is scrubbed out after use.

Disturbed Menstruation after Parturition

Q.—*Since the use of oestrogens to inhibit lactation a multipara of 30 has had irregular periods. There have been two peculiarities; a period has started the day following intercourse on each of the only three occasions since the birth when it has been practised, and the periods have been associated with breast engorgement and the secretion of milk. What is the explanation of these associations?*

A.—Assuming that oestrogens were given only for the usual period of four to eight days and have long been discontinued, their use can be dismissed as having no bearing on the present symptoms. The data imply that the confinement occurred only a few months ago, and it is common enough to see some disturbance when menstruation is resumed—especially if the woman does not breast-feed the baby. Absence of lactation tends to delay involution and to result in a return of menstruation at a time when the uterus is still large and vascular. Extreme congestion of the uterus could result in bleeding after coitus, although the relationship of coitus to menstruation in this case might be coincidental.

Some enlargement and tenderness of the breasts is also common at the time of menstruation, and especially premenstrually. It takes months and sometimes years before secretion disappears entirely from the breasts after pregnancy, and it is likely to be more noticeable at the time of premenstrual engorgement.

The clinical features of this case do not suggest anything which could not be regarded as a minor functional disturbance which is frequently seen after pregnancy—and especially if breast-feeding is avoided. They should settle of their own accord within a few months; if they do not, further investigation will be required.

Medical Hazards of Sand-pits

Q.—*What are the medical hazards of children's sand-pits in public parks? How seriously should such hazards be taken, and what preventive measures are worth while?*

A.—The medical hazards of children's sand-pits are that infections may be spread from pollution of the sand, and that the sand itself may cause injury to the eyes through being blown or thrown about.

Pollution would occur from excretion either by the children themselves or by dogs and cats. The risk of infection being spread from child carriers is very small indeed. The diseases most likely to be involved are the enteric fevers and dysentery. In the former, young children are very rarely found to be carriers, and in the latter a child carrier would almost certainly be a clinical case and would therefore be unlikely to be playing in a sand-pit. Other infections which might be spread through children playing in sand-pits would be due more to the circumstances of their aggregation than to the conditions of the sand-pit itself.

The hazard, though small, should not be neglected. The sand-pit should be adequately fenced and animals rigorously excluded. There should be sanitary accommodation close at hand. The sand should be raked daily to remove surface debris and turned regularly in order to bring moist sand to the surface and to disperse sand that has been polluted. In hot dry weather the sand should be sprayed to reduce the risk of eye injury. Treatment with rock salt has been employed to increase the cohesion of the sand. It is inadvisable to have trees overhanging the sand-pit, as they are likely to reduce the bactericidal action of sunlight, while the fallen leaves tend to produce a compost. Finally, whenever the sand shows signs of becoming dirty it should be removed.

Alcohol and Barbiturates

Q.—*In cases of "drunk in charge" the accused sometimes says that he has taken barbiturates as well as alcohol. Do alcohol and barbiturates potentiate each other?*

A.—Barbiturates and alcohol are both cerebral depressants. Consequently the effect of one will certainly be potentiated by a dose of the other. Whether they are pharmacologically synergistic to one another is more controversial. This question is discussed by Dille and Ahlquist[1] and by Ramsey and Haag.[2]

REFERENCES

[1] *J. Pharmacol.*, 1937, **61**, 385.
[2] Ibid., 1946, **88**, 313.

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